GMP Requirements for Medicinal Cannabis Manufacture

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GMP FORUM 2024

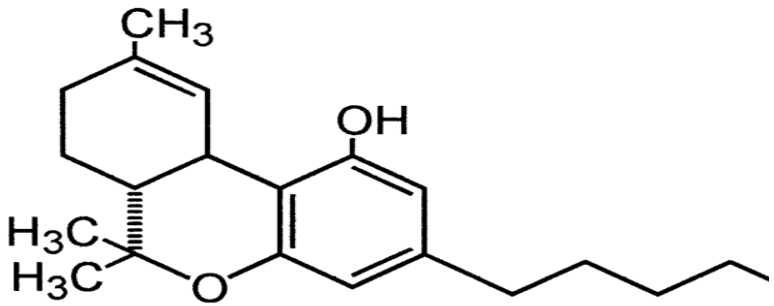
Agenda

- Background/Regulations
- ODC & TGA
- Medicinal Cannabis GMP & Exemptions
- TGO 93/ Overseas Certification
- Licence/Certification requirements/ examples
- Common deficiencies seen

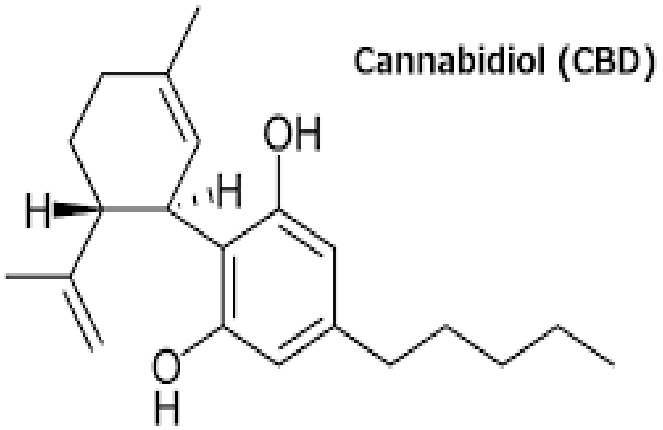
Cannabis - Definition

Cannabis describes all plants of the Cannabis genus. Cannabis includes the **seeds, extracts, resins, and the plant as well as any part of the plant**

- Cannabis plant produces a **resin containing compounds called cannabinoids**
- Two main components reported to have medicinal properties: **delta-9-tetrahydrocannabinol** and **cannabidiol**



△-9-tetrahydrocannabinol (THC



Legislation

Two different pieces of legislation govern the access to medicinal cannabis products:

- The Office of Drug Control (ODC), which regulates controlled substances to prevent diversion and illicit use. ODC administers the *Narcotic Drugs Act 1967*.
- The TGA, which regulates medicines by administering the *Therapeutic Goods Act 1989*

Note: The states and territories have local regulations regarding access to Medicinal Cannabis products to be adhered to when manufacturing and supplying in the relevant state/territory

Scheduling – Poisons Standard (SUSMP*)

Regulatory control: the availability of the medicine or poison, required to protect public health/safety.

- **Schedule 3 (Pharmacy Only Medicine)**: Substances, that do not require a prescription, but they are only available from pharmacies. – e.g., at least 98% CBD of the total cannabinoid content/ less than 1% THC/ Maximum daily dose of 150 mg CBD/ ARTG registered.
- **Schedule 4 (Prescription Only Medicine)**: Substances, the use or supply of which should be by or on the order of persons permitted by State or Territory legislation to prescribe and should be available from a pharmacist on prescription – e.g., cannabidiol containing < 2% other cannabinoids
- **Schedule 8 (Controlled Drug):** Substances which should be available for use but require restriction of manufacture, supply, distribution, possession and use to reduce abuse, misuse and physical or psychological dependence – e.g., nabilone, dronabinol, nabixomols, cannabis, THCs (these can be of natural origin or synthetic)
- **Schedule 9 (Prohibited Substance):** Substances which may be abused or misused, the manufacture, possession, sale or use of which should be prohibited by law except when required for medical or scientific research, or for analytical, teaching or training purposes with approval of Commonwealth and/or State or Territory Health Authorities - Cannabis that do not meet Schedule 4 or 8 are classified as Schedule 9

*Standard for the Uniform Scheduling of Medicines and Poisons

Access Pathways

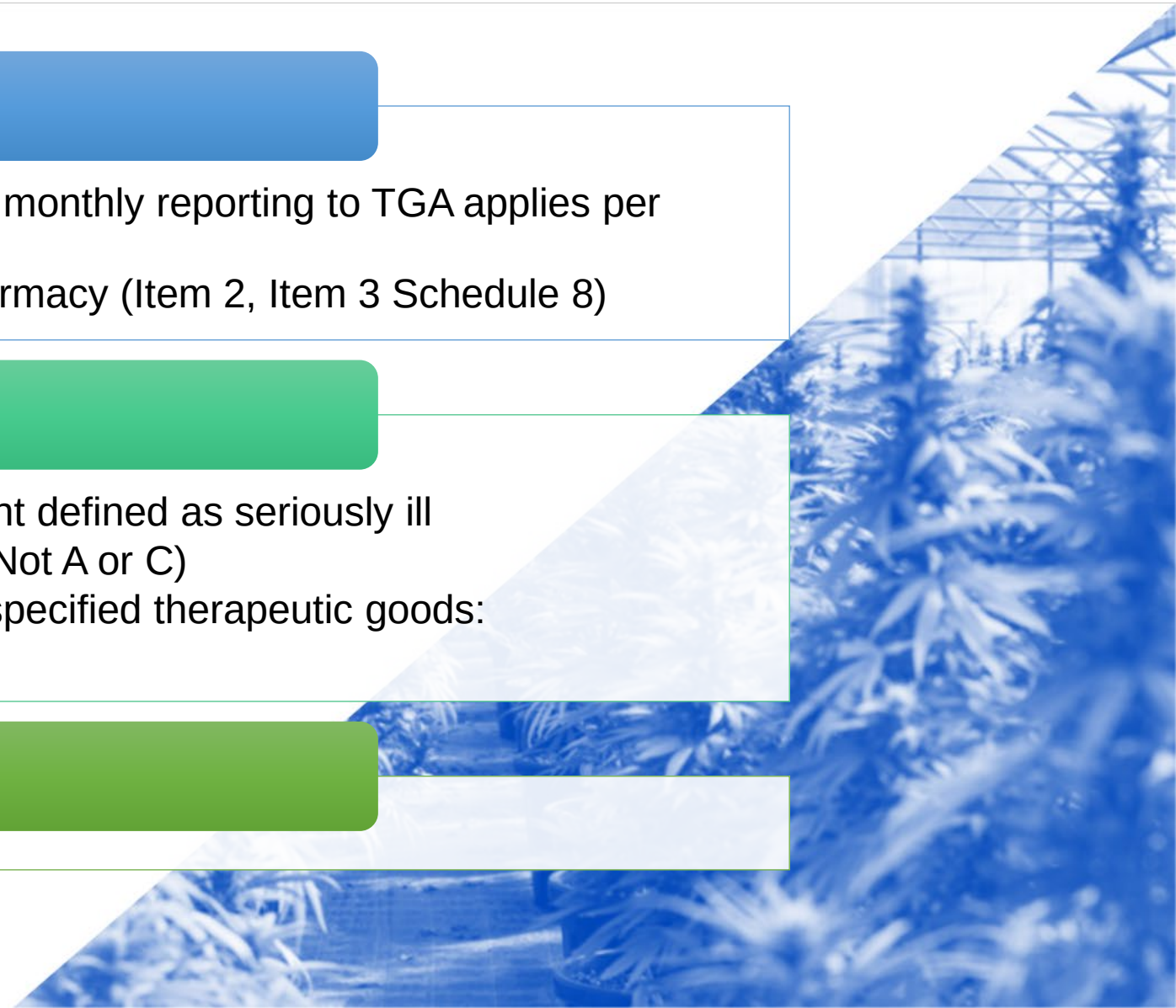
Authorised Prescriber Scheme (AP)

- Applies only to medical practitioners, 6 monthly reporting to TGA applies per product/ imported medicine per patient
- Compounding Pharmacy /Hospital Pharmacy (Item 2, Item 3 Schedule 8)

Special Access Scheme (SAS)

- SAS category A: notification for a patient defined as seriously ill
- SAS category B: application pathway (Not A or C)
- SAS category C: notification of use of specified therapeutic goods: established history

Clinical Trials: CTN/CTX



Differences between TGA and Office of Drug Control (ODC) Licensing

TGA and ODC licences serve different purposes, with some overlap

TGA Licence/Certificate to manufacture

Applicable to

- All steps in manufacture of medicinal product (API & finished goods)
- Clinical trial materials after Phase 1 studies

Exemption from licencing apply for certain APIs, herb preparation & drying, early extractions

ODC Licence or permit to produce & manufacture narcotics

Required for

- Cultivation
- Experimental /research
- Manufacture of extracts/resins including purification/concentration/isolation
- Conversions, including from one Cannabinoid to another
- Import/export Permits

Terminology Can be Similar (TGA/ODC)

Where the terminology is similar (e.g. manufacture) the definitions are quite different under the respective legislations.

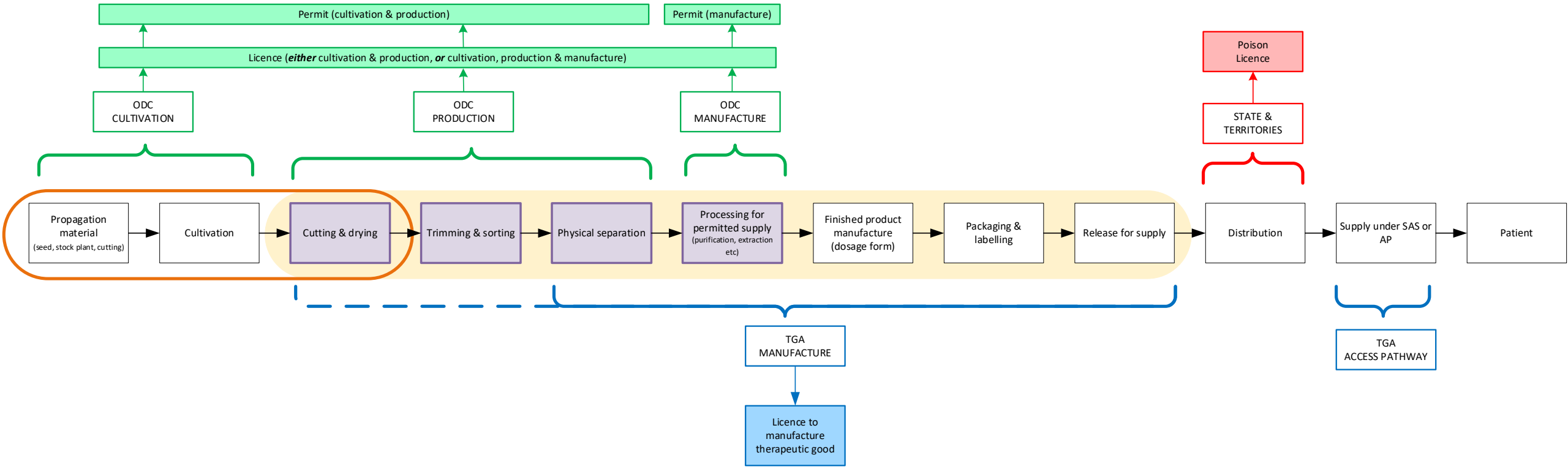
- A TGA GMP licence focuses on the quality of therapeutic goods, whereas the narcotic manufacture licence specifies what drug may be produced and in what quantities.

- Therefore, a manufacturer may require **both** licences. A licence issued under the Therapeutic Act does not remove the requirement for a licence under the Narcotic Drugs Act and vice versa.

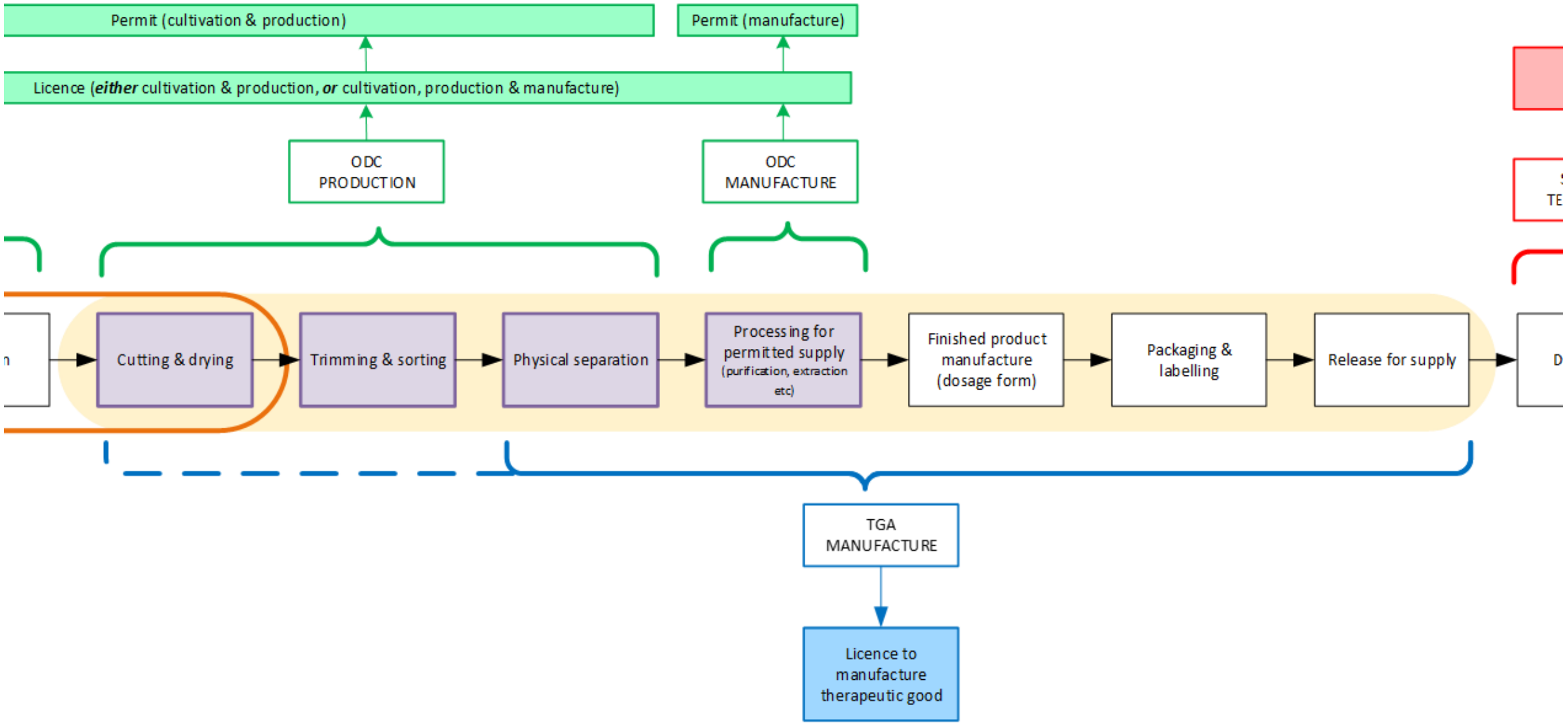
- Also as different states/territories may have different regulations various other local permits may be different between them irrespective of ODC and TGA licensing

TGA and ODC regulatory control overlaps

Cultivation → finished product manufacture conducted in Australia



TGA and ODC regulatory control overlaps



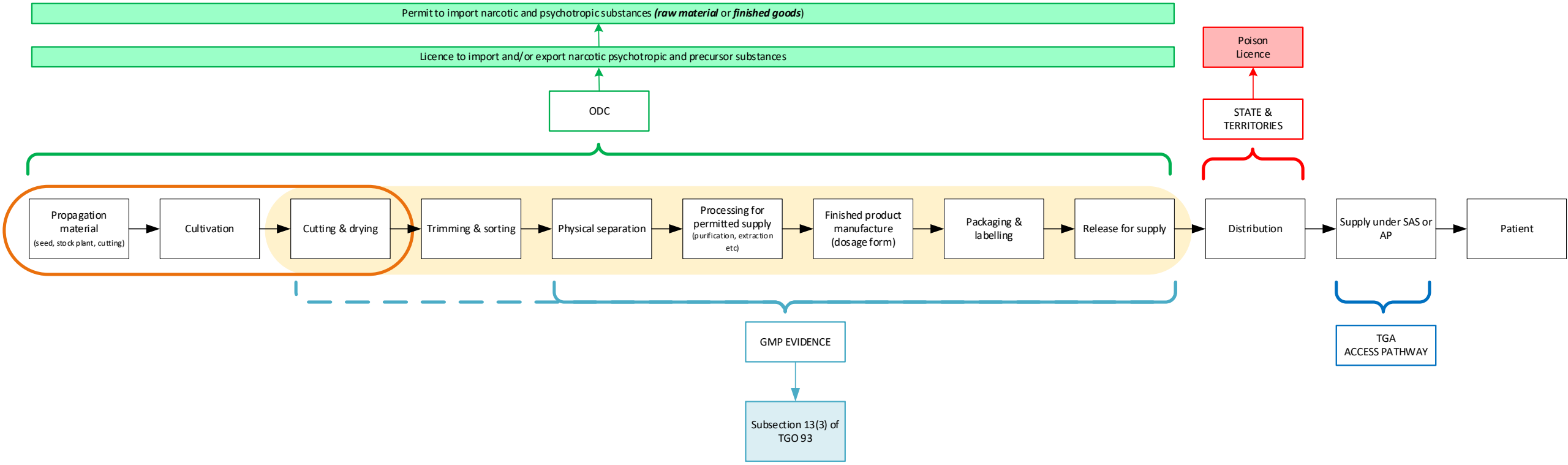
Licences and permits

What licence and permits do I need?

Cannabis manufacturing steps	TGA manufacturing licence	Overseas manufacturing licence/certificate	ODC Licence & Permit	
Propagation materials (e.g., seed, cuttings, plants)	✗	✗	✓	cultivation
Cultivation of cannabis plant	✗	✗	✓	cultivation
Cutting and drying	✗	✗	✓	production
Trimming and sorting	▲	▲	✓	production
First expression e.g., crude extract	✓	✓	✓	manufacture
Further processing	✓	✓	✓	manufacture
Finished product manufacture	✓	✓	✗	
Storage	✓	✓	✓	Cultivation, production & manufacture
Testing	✓	✓	✓	Cultivation, production & manufacture
Packaging and labelling	✓	✓	✗	
Release for supply	✓	✓	✗	

Regulatory controls across the supply pathway

TGO 93 GMP evidence required for imported product



GMP Evidence for Imported Products (TGO 93 sect 13)

- Each step of manufacture outside Australia must be in accordance with GMP.
- Australian sponsor must obtain/hold acceptable written evidence
- TGA will recognise certification by specified foreign regulators

- TGA inspection can be requested (certificate not a clearance)
- ‘Exemptions applies :
  - ‘Starting material’ for this purpose is ‘plant material’; or ‘oil extracted directly from the cannabis plant’ to be used as a starting material at an Australian TGA licenced manufacturer

Licensing Example

A manufacturer conducts an extraction to make cannabis oil solely for use by a TGA licensed manufacturer for producing finished products. This process was exempt from requiring a GMP licence.

The manufacturer decided to conduct steps of further refinement and/or distillation of the oil e.g. concentrating to a high percentage of THC, and wants to supply the oil as a Finished Product. The manufacturer holds an ODC licence. How would this affect GMP licencing?

- The change in manufacturing steps, are considered manufacturing steps where GMP does apply, and TGO 93 for quality control is required. TGA licence is required.

- An ODC Manufacturing licence is also required to be amended as cannabinoids (such as THC or CBD) are being isolated/ concentrated.

Licensing Example

A manufacturer purchased an already extracted API to be refined, isolating THC during purification processes. The final product would be for export only. What licencing may be required?

- ODC licence and permit for export
- TGA licence to manufacture
- Export listing on the ARTG
- TGO 93 does not apply

Licensing knowledge test

A cultivator of medicinal cannabis collected, cut and dried the flower of the plant.
The product was packed in sachets as finished product.
What licences may be required?

- ODC cultivation licence
- ODC manufacturing licence
- TGA licence.

The same manufacturer extracted the harvested plant into a resin
and further decarboxylated to cannabinoids, to be further processed
at another manufacturer under contract.
What licences may be required?

- ODC licence update/conversion step added
- TGA licence variation / possibly new inspection
- TGA and ODC licences (contract manufacturer)

Licensing/OS certification knowledge test

A sponsor would like to import finished cannabis oil to be re-packaged at a contract packaging company and stored at the company site. The product will be prescribed by an Authorised Prescriber and supplied by a pharmacist. What are the licencing requirements?

- The sponsor must hold evidence of compliance of goods to TGO 93.
  This may require a TGA inspection of the overseas manufacturer depending on the country of origin.
- The manufacturer must have a TGA licence for packaging, labelling and release
  for supply as well as storage
- The manufacturer will also require an ODC licence/permit
- The Pharmacist must have a licence to hold/dispense S8 medicines (State/Territories requirements)
- The Authorised Prescriber must have approval from the TGA to prescribe cannabis

Points to Remember

- For a compounding site, all starting material needs to have been manufactured under appropriate GMP
- Australian sponsor must hold GMP evidence, ready to provide to the TGA if requested
- Every participant in the chain needs to be satisfied that a medicinal cannabis product is compliant with TGO 93
- For sections of the cannabis manufacturing process that are exempt from TGA licencing requirements; these activities should be conducted with GMP principles in mind.

Exemptions from Licencing Requirements for some cannabis APIs

GMP principles should be followed for all aspects of the cannabis manufacturing process.

There are some exemptions under Schedule 7 to the Therapeutic Goods Regulations 1990 (the Regulations) that allow the manufacture of therapeutic goods in Australia to occur without a GMP licence, this includes the manufacture of herbal material, (not powdered or milled herbs) or the oil extract from herb under certain conditions*.

These exemptions apply when cannabis plant or extracted oil is used as starting material for further manufacture at a licensed site.

The exemptions allow cultivation sites to grow, cut and dry cannabis and to produce a crude extract for further manufacture without themselves holding TGA licence.

*For overseas manufacture of medicinal cannabis products subsection 13(1) of TGO 93 applies the same exemption for cannabis plant material and the first crude oil extract for overseas manufacturing as Schedule 7

PICS GMP Guide, Part II APIs

Type of Manufacturing	Application (Part II) of the GMP Code				
API extracted (Plant)	Collection of plants	Cutting/ initial Extraction/s	Introduce API Starting material	Isolate Purify	Process & Pack
Herbal extracts (used as API)	Collection of plants	Cutting/ initial Extraction/s		Further Extract.	Process & Pack
API Powdered Herbs	Collection of plants and/or cultivation and Harvesting	Cutting and Commuting			Process & Pack

PICS GMP Guide Annex 7

Activity	Good Agricultural and Collection Practice (GACP) #	Part II of the GMP Guide †	Part I of the GMP Guide †
Cultivation, collection and harvesting of plants, algae, fungi and lichens, and collection of exudates			
Cutting, and drying of plants, algae, fungi, lichens and exudates *			
Expression from plants and distillation**			
Comminution, processing of exudates, extraction from plants, fractionation, purification, concentration or fermentation of herbal substances			
Further processing into a dosage form including packaging as a medicinal product			

Case 1 : Where does licensing start?

A manufacturer of Medicinal cannabis finished product engaged in

- Receiving cannabis flower
- Cutting/trimming/drying the flower
- Extracting via a series of extractions to produce cannabis oil
- The oil is refined and isolated to a CBD/THC concentrate
- Oil bottled as a finished product

Which steps require a manufacturing licence from the TGA?

a. Cutting/trimming/drying the flower
b. first extraction
c. last extraction
d. oil refinement stage

What would change if the oil was produced and distributed as an API for finished product manufacture?

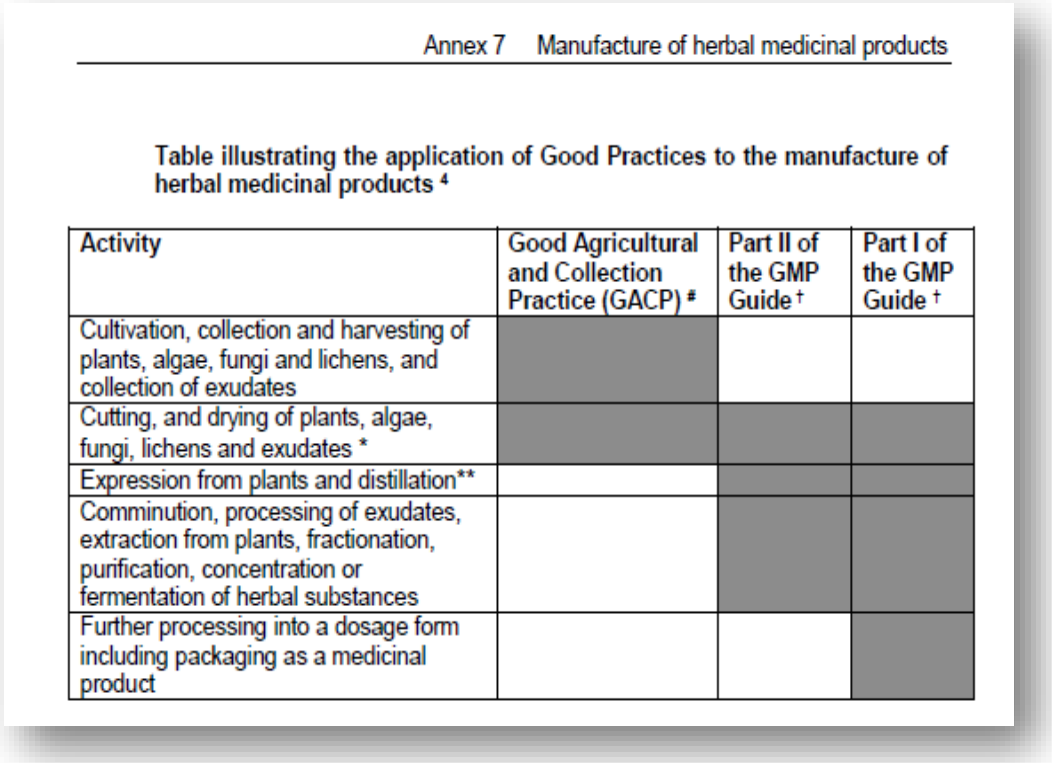
Case 2 : Where does licensing start?

A manufacturer of Medicinal cannabis engaged in

- Receiving cannabis herb
- Cutting, drying
- Milling into a fine powder
- Heating to decarboxylate the herb
- Encapsulating and packaging

Which steps require a manufacturing licence from the TGA?

a. Cutting & drying the flower
b. Milling into a fine powder
c. Decarboxylation
d. Encapsulation



Annex 7 Manufacture of herbal medicinal products

Table illustrating the application of Good Practices to the manufacture of herbal medicinal products [4]

Activity	Good Agricultural and Collection Practice (GACP) #	Part II of the GMP Guide †	Part I of the GMP Guide †
Cultivation, collection and harvesting of plants, algae, fungi and lichens, and collection of exudates			
Cutting, and drying of plants, algae, fungi, lichens and exudates *			
Expression from plants and distillation**			
Comminution, processing of exudates, extraction from plants, fractionation, purification, concentration or fermentation of herbal substances			
Further processing into a dosage form including packaging as a medicinal product			

What would change if comminution (small cut flower) replaced milling to a fine powder?

GMP Requirements

PICS PE009-16

- Applies to medical cannabis manufacture including relevant Annexes.
- Specific attention to Annex 7 (herbal medicinal product manufacture)

TGO 93

Specific quality standard for medicinal cannabis

- Adulteration, decontamination, identification & testing
- Manufacturing quality & specific packaging requirements
- Labelling
- Microbiological attributes

Other applicable TGOs & Guidance Documents

- TGO 101 specific solids dosage forms
- Interpretative documents for application of PIC/S Guide GMP for medicines of natural origin (i.e. some Listed medicine interpretation documents)

GMP Code (PICS PE009-16)

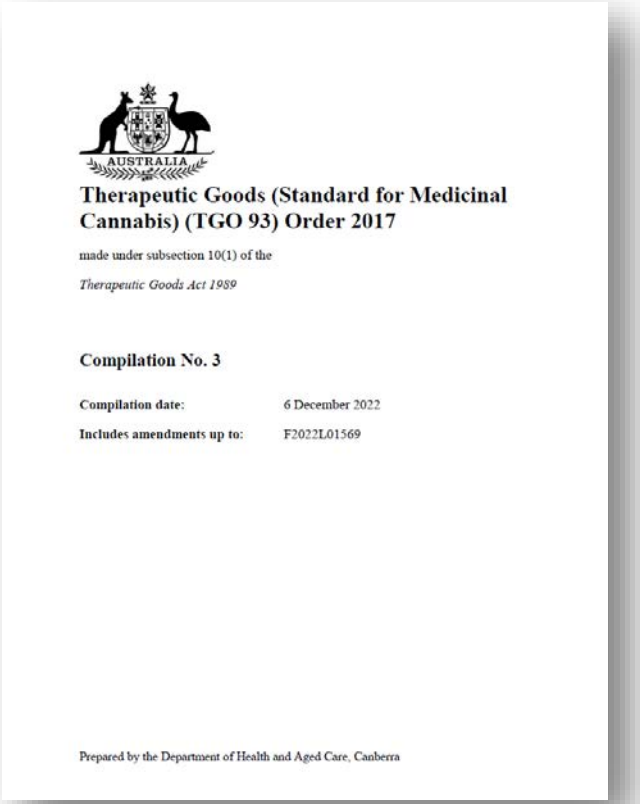
- Personnel/ Training
- Quality System: Deviations, Change Controls, Complaints, Risk assessments, Annual Product reviews, Recalls, self-inspections, returned goods, hygiene and gowning, GMP Agreements, Supplier Approval, Rework, Reprocessing, and others
- Production Processes
- Facility/Engineering –calibration and maintenance
- Utilities- HVAC, water systems, compressed air, gases
- Validation and Qualification documents
- Chemistry and Microbiology testing
- Batch records

Medicinal Cannabis Quality (TGO 93)

Medicinal Cannabis Quality (TGO 93)

TGO 93 sets out the minimum requirements for Product Quality for medicinal cannabis and incorporates the requirements of the various general monographs of the European Pharmacopoeia for herb drugs/extracts:

- Identification Physical/Chromatographic
- Chemical constituents/Assay
- Others: pesticide, aflatoxin, ochratoxin A, heavy metal, total ash, foreign matter
- Microbiology
- Decontamination by ɣ / X ray allowed where product impact is assessed not to adversely affect product quality. Ethylene oxide use is not allowed



AUSTRALIA

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

made under subsection 10(1) of the

Therapeutic Goods Act 1989

Compilation No. 3

Compilation date: 6 December 2022

Includes amendments up to: F2022L01569

Prepared by the Department of Health and Aged Care, Canberra

GMP key points Guidance

Complementary Medicines Guidance Documents can be used:

- Sampling and testing
- Supplier assessment
- On going stability testing
- Validation
- Product quality reviews

Sampling of Starting Materials

Sampling / Supplier assessment

- Allow for reduced sampling when certain requirements are met.

Material type	Pre-qualification	Post qualification
Excipients – starting materials	**$\sqrt{n}+1$**	**Apply $\sqrt{n}+1$ OR** **reduced sampling plan if:** – **material is from a site that manufactures only one product** – **Scientifically justified**
Actives – starting materials	**Sample all containers.**	

Where supplier performance changes/deteriorates then the sampling plan to be reassessed

Process Validation

Qualified equipment is a must

Risk base approach (monitoring critical process parameters, critical quality attributes)

Use statistical tools to justify consistency of process (3 batches unless justified otherwise

For multiple active product - cannabinoids must be tested

Bracketing strategy: by concentration lowest/highest

Visual, color, weight uniformity, assay

Grouping approach (same process/ equipment/ ingredients)

On-going Stability

- Generally, the responsibility of the sponsor
- Supporting product shelf life/covering the Marketing Authorisation
- One product a year from each group of product/justified grouping/rotating representative of the group
- To be assessed when significant formulation/pack change
- Monitor level of impurities/ breakdown
- Always using stability indicating testing methods
- Microbiology testing - start and end of study as minimum

Product Quality Review

a mechanism to ensure that data captured by the Pharmaceutical Quality System (PQS) is reviewed for trends as well as changes affecting all quality elements

Verifies the consistency of process (statistics)/ current specifications

Causes of quality incidents/identify impacts/ identify potential improvements

Annually Conducted unless justified otherwise

Grouping may be used. However all incidents must be considered for all products in the group/trend results.

Recent Common Deficiencies - Vendor Approval

The requirements of Clause 5.27 (Part I) **concerning the selection, qualification, approval and maintenance of suppliers of starting materials** [. . .] was not fully met. For example, **there was insufficient evidence available to demonstrate any of the suppliers of critical materials or goods, which had direct product quality impact, complied with the requirements outlined in Vendor Management procedure**.

Specifically, there was one or more of the following required elements of the vendor approval program missing for all critical suppliers:

- A formal quality agreement.
- Evidence of an audit to confirm that they comply with the relevant good manufacturing practice and good distribution practice requirements.
- Evidence that the first three batches of material received to site had been tested to demonstrate compliance to the company's internal specification.

Recent Common Deficiencies - Vendor Approval

The requirements of Clause 5.27 that the selection, qualification, approval and maintenance of suppliers of starting materials [. . .] were not fully met. For example, the Supplier Approval procedure had not been updated to address the increased risks posed by manufacture of narcotic active substances.

Specifically, the procedure did not include the following requirements as part of the approval and maintenance of suppliers of bulk cannabis dried flower:

a. Appropriate aspects of the production, testing and control, including handling, labelling, packaging and distribution requirements, complaints, recalls and rejection procedures should be documented in a formal quality agreement or specification (also Clause 5.28).

b. Audits should be carried out at the manufacturers and distributors of the active substance to confirm that they comply with the relevant good manufacturing practice and good distribution practice requirements (the holder of the manufacturing authorisation can verify such compliance either by themselves, or through an entity acting on their behalf under a contract) (also Clause 5.29).

Recent Common Deficiencies – Vendor Approval

The requirement of Annex 15, Clause 5.12 that **suppliers of critical starting and packaging materials should be qualified** was not fully met, specifically:

a. **Vendor management procedures** did not state how new vendors are approved, and what criteria was used. Assessment of quality requirements ?
b. There was a **questionnaire** available for supplier assessment, however, the inspector identified it **was not used in every case**.
c. It was unclear how the **testing assessment** was conducted and how many samples/lots were used in the assessments. Supplier examples listed/contract **agreements gaps** also

Recent Common Deficiencies - Document and Data Control

The requirements of Clause 4.1 (Part I) and Clause 6.14 (Part II) that **appropriate controls for electronic documents** such as templates, forms, and master documents should be implemented to **ensure the integrity of the record throughout the retention period**; and when entries are made in **records**, these should be made **indelibly** in spaces provided for such entries, **directly after performing the activities**, and **should identify the person making the entry**, were not fully met. For example,

a. The process for issuance of hard copy forms did not ensure forms were uniquely identified and reconciled to ensure all recorded data was be collected and/or reported, an issued form was not lost, or replaced, without authorisation.

b. Excel spreadsheets were used to record GMP critical data such as the Materials Register, Deviations and Non-conformances Register, and Complaint Register; however, the spreadsheets did not secure data against damage and ensure the integrity of the record, nor did they identify the person making the entry into the register (also Annex 11 §7.1).

Recent Common Deficiencies – Product Quality Review

The requirements of Clauses 1.10 and 1.11 (Part I) regarding Product Quality Review (PQR) were not fully met as the PQR procedure and associated reviews did not include all requirements to ensure that the PQR was consistently performed in a complete and effective manner. For example:

- Guidance or justification for product grouping e.g., dried flower group, oil product group, vape product group, liquid product group
- Reviews of critical in-process control parameters and critical finished product results
- Review of the results of batches placed onto stability
- Performing trend analysis and highlighting any trends
- Review of the qualification status of relevant utilities e.g., HVAC and compressed air

Recent Common Deficiencies - Storage

The requirements of Clause 3.18 that storage areas should be of sufficient capacity to allow orderly storage of the various categories of materials and products were not fully met. For example,

- Segregated areas had not been provided for the storage of rejected, recalled or returned materials or products
- (also clause 3.23)

- No storage area had been designated to ensure reference and retention samples from each batch of finished product was retained for at least one year after the expiry date (also Annex 19 § 3.1).

Recent Common Deficiencies - Recall

- The requirements of Clause 8.30 that the effectiveness of the arrangements in place for recalls should be periodically evaluated to confirm that they remain robust and fit for use were not fully met as the procedure associated with recall of product did not include **a processes to confirm recall effectiveness**

- The requirements of Clause 8.20 (Part I) and 15.13 (Part II) that there should be a written procedure that define the circumstances under which a recall of an intermediate or API should be considered, and be available in order to undertake any recall activity of medicinal product or implement any other risk-reducing actions such as product retrieval from the distribution network as a result of a quality defect, was not fully met as **no recall procedure was available within the Pharmaceutical Quality System (PQS)**

Recent Common Deficiencies in Clinical Trials

The requirements of Annex 13 Principle that investigational medicinal products (therapeutic goods for clinical trials) should be produced in accordance with the principles and the detailed guidelines of PIC/S Guide to GMP were not fully met. For example,

- Requirements for a **Product Specification File were not outlined** within the current PQS and no formal process was documented to ensure **any changes made to the product specifications, manufacturing instructions and in-process testing during development were continually updated as development of the product proceeds**, ensuring appropriate traceability to the previous versions (also Annex 13 §9).

- **No procedures were available to control blinding operations, and the generation, security, distribution, handling and retention of any randomisation code** (also Annex 13 §21 & 22).

Recent Common Deficiencies - Validation

The requirements of Annex 15 Clauses 5.7 and 5.19 that process validation should establish whether all quality attributes and process parameters, which are considered important for ensuring the validated state and acceptable product quality, can be consistently met by the process, and that the number of samples taken should be based on quality risk management principles, allow the normal range of variation and trends to be established and provide sufficient data for evaluation, were not fully met as evidenced by:

- The Process Validation for Oil Manufacture did not contain sufficient evidence to justify that, the **mixing process could perform effectively and reproducibly to produce the bulk oil product meeting its predetermined specifications and quality attributes** in that:
  i. A **sampling plan was not defined**
  ii. There was **no record nor documented evidence to demonstrate that the designed mixing process met the intended purpose**
- **Decarboxylation processes had not been validated**
- Filling validation used for 30, 50 and 100mL oil bottle sizes was conducted and approved based on acceptable in-process test results during filling. **There was no review and conclusions of the validation reported, and no results summarised against the acceptance criteria**

Recent Common Deficiencies - Validation

The requirements of Annex 15, Clauses 10.1 and 10.6 that **cleaning validation should be performed to confirm the effectiveness of any cleaning procedure for all product contact equipment; simulating agents may be used with appropriate scientific justification** and **to assess carryover residue limits**, were not fully met as there was no complete cleaning validation study was available; there was no justification supplied for the reliance on visibly clean verification, a pH neutral test and an ATP swab test.

a. The use of pH as a measure of cleaning check is also indicative for removal of alkaline soapy cleaning agent; not suitable to detect residue level/cleaning effectiveness.

b. 6 monthly surface swabbing after potable water clean; this was insufficient to demonstrate the water was suitable for cleaning contact surfaces.

Recent Common Deficiencies - Validation

The requirement of Annex 15, Clause 5.7 that **process validation should establish whether all quality attributes and process parameters, which are considered important for ensuring the validated state and acceptable product quality, can be consistently met** by the process was not fully met. For example,

a. Process validation protocol of the broad spectrum API was available, however, the validation study had not been completed. The protocol was unclear regarding sampling locations and testing to show homogeneity. (no statistical tools used).

b. Mixing and bottle filling process validation was in progress; there was no validation protocol as the batch records were used in lieu of. Consistency of the batches could not be assessed as minimal data was collected to ensure process validation.

Recent Common Deficiencies - Investigations

The requirements of Clauses 1.8vii and 1.9iv (Part I) and Clause 2.16 (Part II) that **any significant deviations are fully recorded, investigated with the objective of determining the root cause and appropriate corrective and preventive action implemented** were not fully met as evidenced by:

a. Systems and related procedures regarding deviations, incidents and non-conformance reporting did not detail how the related investigations were conducted to ensure the root cause of issues was determined.
b. Example detailed potential sources of contamination, but did not include all known contamination sources.
c. Example, in relation to “messed up lot numbers”, did not detail the potential root causes to ensure suitable corrections were implemented.
d. Example of foreign matter on top of droppers as well as bottles; these were disposed of; did not include an investigation to show origin of the matter to make a suitable correction and prevention/ suppler was not involved.

Recent Common Deficiencies - Training

The requirement of Clause 2.11 that besides the basic training on the theory and practice of the Pharmaceutical Quality System and Good Manufacturing Practice, newly recruited personnel should receive training appropriate to the duties assigned to them; and **continuing training should also be given, and its practical effectiveness should be periodically assessed,** was not fully met as evidenced by:

a. Training procedures did not cover the criteria for training assessment and when using a quiz. The pass/fail criteria and retraining requirements were not detailed to ensure consistency. .
b. In some cases the training attendance record was considered sufficient as a measure of training assessment. There was no clear training effectiveness recorded.
c. Training was ineffective for all, as reoccurring errors were identified in different areas and processes by staff, which indicated training was ineffective for all.

Summary

- Regulations
- ODC and TGA – differences & similarities
- Medicinal Cannabis and GMP exemptions
- TGO 93 and Overseas Certification
- Licence/Certification requirements
- Common deficiencies

Questions?

Scan this QR code with your device to submit a question

GMP FORUM 2024

Australian Government

Department of Health and Aged Care

Therapeutic Goods Administration