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REGULATORY FRAMEWORK AND CLINICAL EVIDENCE FOR MEDICINAL CANNABIS PRODUCTS

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The government's intent

- Provide **patient access to Australian-grown and manufactured medicinal cannabis** outside the standard registered medicines route
- **Provision of a quality medicine** through doctors prescription
- **Encourage clinical trialling** for potential future TGA registration
- The **Health Products Regulation Group has oversight**
  - Cultivation and manufacture (Office of Drug Control)
  - Product GMP, product scheduling and patient access through the Therapeutic Goods Administration (TGA)
- **States and Territories** also have a role in regulation

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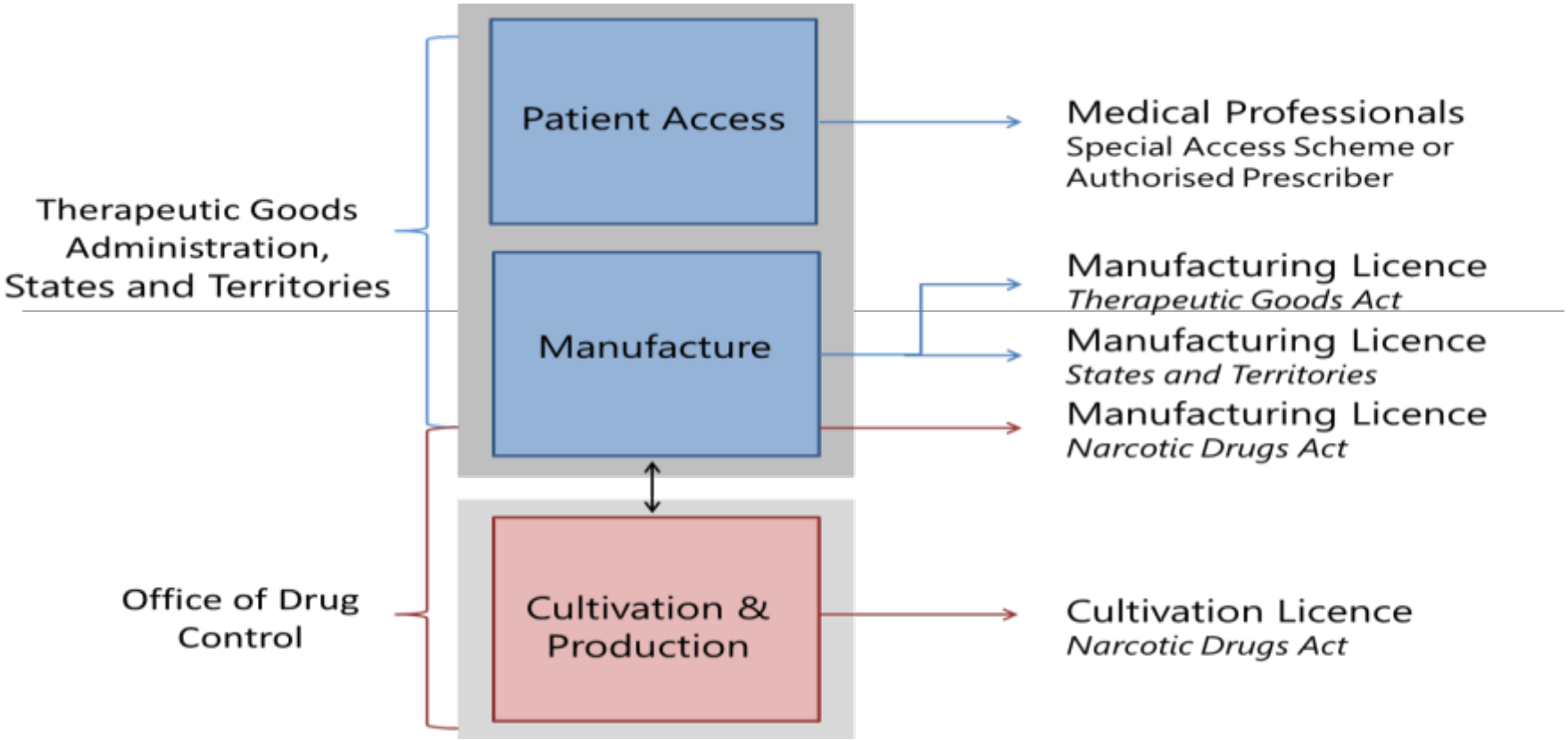

Regulating cultivation and manufacture

- In 2016, Government **amended the *Narcotic Drugs Act 1967*** to
  - allow cannabis to be treated as a medicine
  - provide for cultivation, manufacture and trade of medicinal cannabis
- Controlling the **production of a narcotic drug**
  - Cultivation and manufacture licences and permits, quality requirements
  - Fit and proper persons requirements, Security and inspections
- Controlling the **import and export of narcotics**
  - Sponsored import of “bulk” medicinal cannabis products
  - Patient by patient imports and travellers’ exemption

Cannabis licence types

- **Four types of licences:**
  - **Medicinal cannabis (cultivation) licences**
  - **Cannabis research licences, manufacturing licences and import licences**
- Under the ***UN Single Convention on Narcotic Drugs*** cultivation for medicinal purposes can only occur under Australian Government licences
- **Permits** (under individual licences) allow the Government to restrict how much is cultivated and manufactured to prevent accumulation

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Licences, permits and bulk imports

- **21 licences granted** as at 10 October 2017, including:
  - 9 Medicinal cannabis licences (cultivation and production)
  - 6 Cannabis research licences (cultivation and production)
  - 6 Manufacture licences
- **Applications for licences are still being received** and processed
- 3 applications for **permits** under licences have been granted thus far
- **Sponsored imports of bulk products** to reduce cost and delays involved in individual importation

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Individual importation of medicinal cannabis

- **Medical practitioners** can arrange patient by patient importation to fill prescriptions issued using TGA SAS A
  - Requires a licence under the *Customs (Prohibited Import) Regulations 1956*
- **Individual patients** can utilise travellers' exemption
  - to carry up to 3 months supply of medicines with them on a ship or aeroplane entering into Australia with a valid doctor's prescription
  - Prior State Health Department approval may also be required

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Concerns about quality of cannabis products

- Variation in **cannabinoid content**, in particular of active ingredient(s)
- Contamination with **pesticides, microbe, mycotoxins**
- Contaminants arising from the **manufacturing process** e.g. solvents
- Adulteration with **synthetic psychoactives, synthetic THC**

TGA has introduced controls

- **Therapeutic Goods Order 93** sets out minimum requirements for the quality of products and raw materials
- **Medicine GMP requirements** on the manufacturing process

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Medicinal cannabis products are available through “unapproved products” pathways

- **Authorised prescriber**
- **SAS A - notification pathway** for patients who are seriously ill with a condition from which death is reasonably likely to occur within a matter of months, or from which premature death is reasonably likely to occur in the absence of early treatment
- **SAS B - application pathway** for patients that do not fit SAS A and where the product is not included on the list for SAS C notification
- For help 800 220 007/ 02 6232 8866, medicinal.cannabis@health.gov.au

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SAS B and Authorised Prescriber

Criteria depend upon the patients, product, prescriber

Authorised Prescribers must:

- have training and expertise appropriate for the condition and the proposed use of the product, and
- be able to best determine the needs of the patient and to monitor the outcome of therapy

Patient and clinical justification

- patient information, diagnosis and indication treated
- the seriousness of the condition
- details of past treatment
- expected benefits from the use of the product

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Product details

- Trade name - Manufacturer/Company/Supplier
- Dose Form i.e. tablet, extract and active ingredients
- Shelf-life and Storage Conditions
- Compliance with TGO 93 for composition / contamination

Administration details

- Dosage, Route of administration, Duration of treatment

Monitoring Detail:

- Efficacy of the treatment, adverse events/reactions
- Human studies to demonstrate efficacy and safety data
- Evidence levels depend on seriousness of the condition

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Notifications (SAS A) and Applications (SAS B and AP)

1 January 2016 to 10 October 2017

SAS A Notifications

- 5 since June 2017 disallowance

SAS B Applications

- Approved applications -173 (rest pending further information or withdrawn)
- 74 for cannabidiol, rest for THC/ CBD in various ratios
- Range of dosage forms for products

Authorised Prescriber Applications

- Approved – 27 (and pending – 6) (101 patients to June 2017)

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Community hope and belief

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Clinical evidence reviews

- **Conducted by team** from U NSW, U Sydney, U QLD and collaborators
- Focus on epilepsy, MS, pain types, nausea and vomiting and palliative care
- Systematic reviews of **published reviews** and **findings of individual studies** using Medline, Embase, PsycINFO, and EBM Reviews
- **Studies published** from 1980 to early 2017
- **Priority was given to RCTs but also included observational studies,** e.g. case reports, retrospective chart reviews, self-report surveys
- Anticipated that **these reviews will be published in the next few months** in international journals – currently being reviewed

Epilepsy

- Five RCTs and 17 observational studies were identified - **all examined CBD as adjuvant treatment** (in addition to standard antiepileptic drugs)
- **Randomised controlled studies**
  - In patients with paediatric-onset drug-resistant epilepsy CBD products reduced seizure frequency and achieved seizure freedom compared with placebo
  - 14% of patients withdrew because of treatment-related adverse events
  - Doses of cannabidiol required were reasonably high (20mg/kg/day)
- **Observational studies:**
  - In 14 of 17 studies, 56% of patients reported reductions in seizures of 50% or more.
  - In 7 paediatric studies 13% were estimated to be seizure-free
  - 10 studies reported improved quality of life in paediatric and adult groups

Cancer and HIV induced nausea and vomiting

- 11 met inclusion criteria, but were mainly against old medicines
- In **managing CINV in adults**, THC/ analogues were more effective than placebo, and as effective prochlorperazine at completely controlling nausea and vomiting, and controlling/reducing nausea
- Comparison of cannabinoids against **newer antiemetics** is required
- Research on cannabinoids for **CINV in children** is more limited
- Evidence of efficacy of cannabinoids in treating **nausea and vomiting in late stage AIDS and terminal cancer** was equivocal

Palliative care

- 9 double blind or open label RCTs studies with a total of 1561 participants were included, but evidence was low quality
- **In cancer patients**, there were **no significant differences** between cannabinoids and placebo for improving caloric intake, appetite, nausea/vomiting, pain, dizziness, mental health or sleep problems
- **In HIV patients**, cannabinoids were superior to placebo for weight gain and appetite but not for nausea/vomiting
- **No convincing evidence** suggesting that cannabinoids are of value for anorexia or cachexia (weakness and wasting) in cancer or HIV

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Multiple sclerosis

- **Nabiximols are TGA approved** for the use in MS for muscle spasticity.
- 11 systematic reviews with data from 32 studies with 3146 patients.
- These included 10 moderate/high-quality RCTs, that examined if cannabinoids reduced pain and spasticity.
- Five reviews concluded that there was **evidence that cannabinoids** may be effective for symptoms of **pain and/or spasticity** and positive effects on **sleep and bladder symptoms**
- **Mixed findings** were reported on quality of life, ataxia/tremor and disability/disease progression
- A **lack of studies** with non-cannabinoid comparators is a major evidence gap

Chronic non-cancer pain

- 102 trials of all types of study designs considered
- Most studies with nabiximols, THC/ analogues, THC-rich preparations
- Most evidence on cannabinoids was from studies where **cannabinoids were adjuvant interventions and not first line treatments for pain**
- Patients who had cannabinoids for **MS-related neuropathic pain** were more likely to experience a 30% reduction in pain (low confidence) and decrease in pain scores (moderate confidence)
- patients who had cannabinoids for **non-MS related neuropathic pain** were more likely to experience a 50% reduction in pain and a reduction in pain scores
- **Insufficient information** to make a conclusion about cannabinoids for the treatment of pain associated with **arthritis and fibromyalgia**

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Draft clinical guidance documents

- **Draft "clinical guidance documents"** for the use of cannabinoids are being developed for epilepsy, MS, pain types, nausea and vomiting and palliative care
- **Decisions on patient access** to particular cannabis products will be made by the treating physician with clinical oversight from the state/territory health departments and TGA
- **Aim to documents by end 2017** with input by Australian clinical experts and patient groups