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REGULATORY REQUIREMENTS:
CLINICAL TRIALS, ACCESS TO UNAPPROVED MEDICINES AND THE TGA REGISTRATION PROCESS

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Medicinal Cannabis and Psychoactive Plants for psychiatric and substance use disorders - this talk

- **Regulation**… it's all about legal access for researchers and patients to these substances
- **Importing substances** for trials
- **Clinical trials**
- TGA **Special Access Scheme** and **Authorised Prescriber**
- **Medical cannabis** access in Australia
- **State and Territory** requirements
- Pathway to **registration as medicines**
- **Medicines scheduling**

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Importing medicinal cannabis and psychoactive plant substances into Australia

- Imports of narcotics, psychotropic substances, drug precursors are controlled under the *Customs (Prohibited Imports) Regulations 1956*
  - administered by the Office of Drug Control
- Narcotic and psychotropic drugs require a licence (valid up to 12 months)
- A permit is also required for each importation for animal research, clinical trials or special patient access

www.odc.gov.au/application-forms#import

www.odc.gov.au/sites/default/files/guidance-import-permit-applications-narcotic-and-psychotropic-substances.pdf

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Unapproved medicines can be used in clinical trials and provided to patients in certain circumstances

- In most cases, therapeutic goods (such as prescription medicines) **must be first approved by TGA** to be lawfully supplied
  - Exceptions are clinical trials, Special Access or Authorised Prescriber Schemes
- Unapproved goods have **not** been evaluated by the TGA for quality, safety or efficacy
- **Cannot advertise** an unapproved medicine to doctors or the public
  - Cannot advertise SAS products at all
  - A clinical trial sponsor is able to promote the trial publicly but cannot specifically mention the name of the medicine being used in the trial

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TGA's role with trials differs from other regulators

- Our main focus is on **access to the unregistered medicine/s** for conducting trials rather than end-to-end regulation of clinical trials
- A **Human Research Ethics Committee** (HREC) is responsible for assessing validity of the trial design, safety and efficacy of the product and the ethical acceptability of the trial protocol
- **A Clinical Trial Notification (CTN)** then just has to be made online to TGA
  - In some cases TGA clinicians informally review protocols, e.g. first in man trials
- **Certain trials (e.g. genetically modified cells) require CTX approval**
  - or are specially referred to TGA for review by the HREC

- **No requirement for trials to be conducted in Australia** for a product to be submitted for regulatory review to TGA
  - Trial population should be similar to Australians
- The Investigational Medicinal Product and placebo **must comply with GMP standards** and the facility must be licensed
  - First in man trials are exempt, but easier to move to phase II/III if a GMP product is used for all phases
  - Products synthesised or purified in research labs are generally not made under GMP

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Legal responsibilities

- **All trials must have an Australian sponsor** - initiates, organises and supports a clinical study and carries the medico-legal responsibility
  - If there is a **major protocol change** a new notification to TGA may be required
- **TGA has the authority to inspect clinical trials**
- **Sponsor responsible** for reporting adverse events during trials directly to TGA
  - See the Australian Clinical Trial Handbook www.tga.gov.au/sites/default/files/australian-clinical-trial-handbook.pdf

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Patient access to unapproved medicines is possible (outside of a clinical trial)

Requires applicant to explain why a currently-approved medicine cannot be used for the treatment of the individual patient

- **Authorised prescriber route -** doctor is approved for a particular indication or set of conditions by a hospital ethics committee, may may prescribe to an unlimited number of patients
- **SAS A - notification pathway** for patients who are seriously ill with a condition from which death is reasonably likely to occur soon
- **SAS B - application pathway** for patients that do not fit SAS A

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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 levelsl depend on seriousness of the condition

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SAS online system

- **SAS online system** enables prescribers in all states to submit applications to access medicinal cannabis
  - simultaneously to TGA /state health department (except Tas)
  - Many fields can be pre-populated
- **Processing time** is **under 2 days**
  - except where the applicant has provided incomplete information
- **State/ territory role** is to check the prescriber, dispenser and patient appropriateness for S8 controlled drugs

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Why are the SAS or AP schemes required for medicinal cannabis?

- Medicinal cannabis products **have not been assessed** for safety, quality and efficacy in the usual manner, and most have not been approved as medicines anywhere else in the world
- **Additional safeguards** of the SAS and AP checks:
  - that products are of acceptable quality, patient indications well defined
  - reduces doctor exposure to significant medico-legal liability
- **State/ territory laws** also require individual assessment of the doctor and patient for diversion or dependency risks for THC containing medicines

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Clinical guidance and medicinal cannabis

- **Clinical guidance documents and literature summaries** for epliepsy, MS, CINV, pain and palliative care at
  www.tga.gov.au/medicinal-cannabis-guidance-documents
- But there is no list of “permitted conditions”

  SAS approvals have already been provided for over 40 indications, including l mood / psychiatric conditions
- 8000-9000 prescriptions have been written in Australia for medicinal cannabis products

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Registering a new medicine

Dossier of safety and efficacy data to be supplied by applicant

Nonclinical data

Evaluated by toxicologists and pharmaceutical chemists

- **Pharmacology data** – laboratory studies investigating efficacy
- **Pharmacokinetic data** how the drug is processed by the body
- **Toxicology data** laboratory/ animal data investigating safety

Clinical data

Usually evaluated by a medical doctor

- **Results of clinical trials** conducted by pharmaceutical companies and/or hospitals or research organisations
- Main focus is on **risk of harms versus benefits**

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Dossier of Product Quality Data also to be supplied by applicant

Evaluated by chemists, biochemists, microbiologists and others at the TGA

- the composition of the substance and the product
- batch consistency
- stability data
- sterility data (if applicable)
- the impurity content

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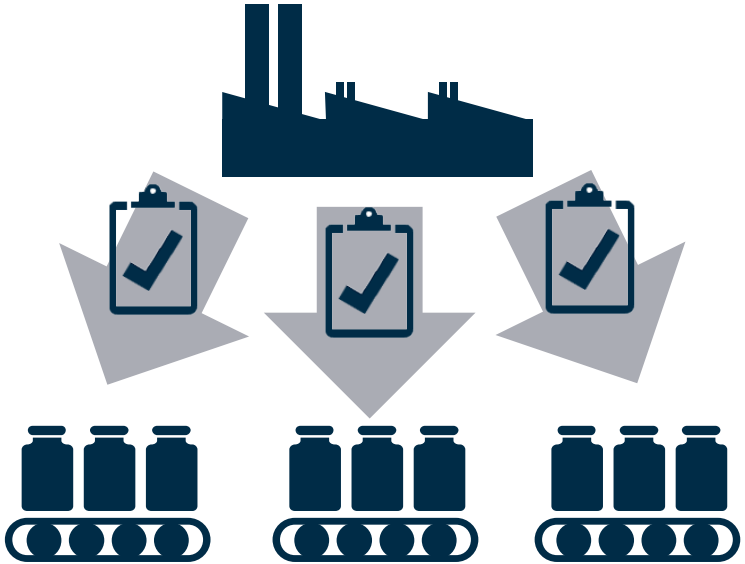
GMP (Good Manufacturing Practice)
facilities where the medicine is made

Evaluated by GMP inspectors in person or through desk clearances

- Simply testing product after manufacture is **not sufficient** to ensure quality
- **Quality must be built into each batch** of a product during all stages of the manufacturing process
- **GMP requirements** cover how products are manufactured, tested, packaged, labelled and stored



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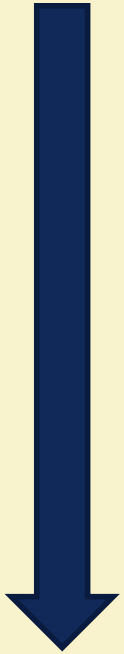
Steps during the medicines evaluation process



Pre-submission meeting of applicant with the TGA

Submission made and accepted by the TGA

First round evaluation → s.31 questions sent to applicant

Sponsor to address questions raised

Responses reviewed → second round evaluation (as required)

Delegate's overview prepared

Submission reviewed by Advisory Committee for Medicines

Decision to be made by TGA Delegate

If approved - Patent certification, Certified Product Details, PI/CMI

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Expedited pathways for regulatory review

- If a serious condition and major advance vs existing products:
  - **Priority Review** of a complete data dossier within 150 working days
  - **Provisional Approval** on the basis of early data on safety and efficacy, where *'promising evidence from early clinical data'* outweighs the risk that additional data is still required
- **COR-A pathway** where the same medicine has been approved by another regulator and the evaluation reports are available
  - 120 working days for recently-approved medicines

Medicines scheduling

- Scheduling classification sets the level of control on the availability of substances (“poisons”) to the general public
  - determined by a senior TGA medical officer, following advice from an expert committee and public consultation
  - but implemented through State and Territory legislation
- Medicines are either
  - Unscheduled (available in supermarkets)
  - Schedule 2 (pharmacy only) or 3 (pharmacist only)
  - Schedules 4 (most prescription medicines) or 8 (controlled drugs)
  - Schedule 9 (only for teaching, training or research including clinical trials)

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Scheduling status of psychoactive substances would need to be reviewed before wider medical use

- A **schedule 9 substance** cannot be provided through SAS A
  - Can be provided through TGA SAS B and Authorised Prescriber - although additional state and territory permissions are required
- Several **psychoactive substances are currently in Schedule 9**
  - MDMA - 5-METHOXY-3,4-METHYLENEDIOXYAMFETAMINE
  - Psilocybin, LSD , DMT - N,N-DIMETHYLTRYPTAMINE
- Scheduling **can be changed on application to the TGA**, supported by evidence e.g. until 2015 cannabis was S9
  - CBD now S4 and THC now S8
  - **Scheduling is re-considered** if a product is under review by TGA for registration