External Evaluations of prescription medicines

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Presented by: Clinical Evaluation Sections, Prescription Medicines Authorisation Branch
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Overview

• Role of the TGA
  – Where the TGA fits into drug development and the health system
  – Structure of the TGA's Clinical Evaluation Sections

• Types of applications
  – The Dossier

• The Clinical Evaluation
  – Role of the clinical evaluator
  – How is the Clinical Evaluation Report (CER) used
  – The CER Template
  – What makes a good clinical evaluation
  – Guidelines
  – Evaluation Timelines
  – Interaction with the TGA

• Resources
Role of the Therapeutic Goods Administration (TGA)

• National regulator of therapeutic goods
  – *Therapeutic Goods Act* 1989
  – Regulates medicines, devices and biologicals

• Medicines include:
  – **Prescription medicines**
  – OTC medicines
  – Complementary medicines

• Regulation of medicines is broadly divided into:
  – **Pre-market regulation**
  – Post-market regulation
The TGA in context

- **Pharmaceutical companies (‘sponsors’)**
  - Drug discovery, quality / manufacturing aspects, non-clinical studies, clinical studies (Phases I-IV)

- **The TGA**
  - A therapeutic good must be registered before becoming generally available
  - The TGA:
    - Receives applications from sponsors to register medicines
    - Assesses quality, safety and efficacy data provided by the sponsor
    - Makes a decision to approve or reject an application, within a set period of time

- **The PBS**
  - Reimbursement of medicines is not considered by the TGA

- **Clinical use**
### Structure of the TGA’s Clinical Evaluation Sections

<table>
<thead>
<tr>
<th>Section 1</th>
<th>Section 2</th>
<th>Section 3</th>
<th>Section 4</th>
<th>Section 5</th>
<th>Section 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychiatry</td>
<td>Infectious diseases</td>
<td>Cardiology</td>
<td>Oncology</td>
<td>Endocrinology</td>
<td>Haematology</td>
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<td>Neurology</td>
<td>Immunology</td>
<td>Metabolic</td>
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<td>Ophthalmology</td>
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<td>Gastroenterology</td>
<td>Vaccines</td>
<td>Male reproductive</td>
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<td>Fluids and electrolytes</td>
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<td>Dermatology</td>
<td>Radiopharmaceuticals, contrast agents, etc</td>
<td>Musculoskeletal</td>
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<td>Fertility</td>
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<td>Nutrition</td>
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<td>Poisoning</td>
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<td>Bone</td>
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Clinical Evaluation Sections sit within the TGA’s Prescription Medicines Authorisation Branch (PMAB)
### Application types

<table>
<thead>
<tr>
<th>New chemical / biological entities (NCEs) Application type A</th>
<th>New fixed combination Application type B</th>
<th><strong>Extension of indication</strong> Application type C</th>
<th>New generic medicine Application type D</th>
<th><strong>New dosage form</strong> Application type F</th>
<th>etc.</th>
<th>Variation to existing ARTG entry (s9D)</th>
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<tbody>
<tr>
<td>Application type A</td>
<td>Application type B</td>
<td>Extension of indication Application type C</td>
<td>New generic medicine Application type D</td>
<td>New dosage form Application type F</td>
<td>etc.</td>
<td>Product Information (PI) change, requiring evaluation of clinical, nonclinical or bioequivalence data Application type J</td>
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<td>Other variation, requiring evaluation of clinical, nonclinical or bioequivalence data Application type H</td>
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<tr>
<td>Module</td>
<td>Contents</td>
<td>Relevance for clinical evaluator</td>
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<td><strong>Administrative Information</strong></td>
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<td>Product Information!</td>
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<td>RMP *(find ‘Safety Specification’)</td>
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<td>Justifications for absence of data</td>
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<td>Overseas registration status</td>
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<td>2</td>
<td><strong>Summaries</strong></td>
<td>Good general overview – from sponsor’s view!</td>
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<td>3</td>
<td>Quality i.e. chemistry / biology / quality</td>
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<td>Nonclinical data i.e. <em>in vitro</em> data, *in</td>
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<td>5</td>
<td><strong>Clinical data</strong></td>
<td>Pharmacology, efficacy, safety</td>
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</table>
The Dossier (II)

in Dossier; evaluated

e.g. relevant journal articles

in Dossier; not evaluated

e.g. efficacy data from studies in patient populations not covered by the indication

not in Dossier; evaluated

e.g. relevant information from past applications; reviews by overseas regulators; literature reviews

not in Dossier; not evaluated (but informative…)

e.g. relevant information from past applications; reviews by overseas regulators; literature reviews
The Dossier (III)

• The size of the Dossier varies from application to application:
  – NCE Dossiers are generally large
  – New indication Dossiers may have only one clinical study (but might have more)

• The CER will vary in size accordingly
  – The template guidance discusses the optimal size of the report

• The Dossier is fully electronic so there are some IT requirements for the evaluator
Role of the clinical evaluator

- To evaluate clinical aspects of the application and write a Clinical Evaluation Report (CER)

- The Clinical Evaluation Report:
  - **Summarises AND CRITICALLY APPRAISES** the clinical data
    - PHARMACOLOGY
    - EFFICACY
    - SAFETY
  - **Asks questions** about clinical data, to be answered by the sponsor; and evaluates answers
  - **Provides recommendations** to the TGA decision-maker about:
    - Whether the drug should be approved or rejected
    - Whether the Product Information is acceptable

- The clinical evaluator **DOES NOT**:
  - Evaluate non-clinical data
  - Evaluate quality data
  - Evaluate cost-effectiveness
  - Make a final decision about registration
How is the CER used? (I)

- The report is used by many parties:
  - The **DELEGATE** (i.e. the decision-maker, who is a senior medical officer in the TGA)
  - **Other sections** of the TGA (e.g. chemistry, toxicology, Risk Management Plan areas)
  - Used for **evaluations of future applications**
  - Submitted to **Advisory Committee on Medicines** and read by committee members
  - Sent to the **sponsor**, where it is reviewed in detail
  - Part of **AusPAR on TGA website**
  - Possibly, other (international) regulators

- Thus, needs to be of **high standard and able to withstand scrutiny**
How is the CER used? (II)

**Sponsor’s information:**
- Dossier
- Answers to questions
- Pre-ACM response
- Post-ACM negotiations

**TGA’s evaluation of Dossier**
- Quality
- Nonclinical
- Clinical

**Risk Management Plan**

**Other information**
- OS regulators (evaluations, PIs, safety reviews)
- Literature
- Clinical practice guidelines
- Past applications
- Public health context

**DECISION OF THE DELEGATE for the given application**
The CER Template (I)

- There is a template to aid with writing the Clinical Evaluation Report
- There is a guidance document that accompanies the template (this is very helpful!)

- There is a single template that covers CERs for all application types, so it may appear quite complex – BUT not all parts are relevant to every application
  - For example, an ‘extension of indications’ application might not have any pharmacology data
The CER Template (II)

- The main headings of the template are:
  - Submission details
  - Background
  - Contents of the clinical dossier
  - Pharmacokinetics
  - Pharmacodynamics
  - Dosage selection
  - Clinical efficacy
  - Clinical safety
  - 1st round benefit / risk and recommendations on registration / PI
  - Clinical questions (to sponsor)
  - 2nd round evaluation
  - 2nd round benefit / risk and recommendations on registration / PI
The CER Template (III) – pharmacology

- Pharmacokinetics
  - ADME
  - Special populations (e.g. hepatic impairment)
  - Drug interactions
  - Population PK

- Pharmacodynamics
  - Mechanism of action
  - Exposure-response

- NCE applications may contain many pharmacology studies

- For some areas, e.g. Population PK, separate expert advice may be required
The CER Template (IV) – efficacy

- There are pivotal and supportive studies in most Dossiers
- For a given study, the elements to consider when evaluating efficacy include:
  1. Study design, objectives, locations and dates
  2. Inclusion and exclusion criteria
  3. Study treatments
  4. Efficacy variables and outcomes
  5. Randomisation and blinding methods
  6. Analysis populations
  7. Sample size
  8. Statistical methods
  9. Participant flow
  10. Major protocol violations/deviations
  11. Baseline data
  12. Results for the primary efficacy outcome
  13. Results for other efficacy outcomes
  14. Evaluator commentary

- There may also be analyses performed across trials
- Your overall conclusion on efficacy should take into account all studies
The CER Template (V) – safety

The type of safety information available from a clinical trial typically includes:

- Exposure to the medicine of interest
- Adverse Events (AEs)
  - overall incidence
  - treatment-related AEs
  - mild, moderate, severe, life-threatening
- Deaths and Serious Adverse Events (SAEs)
- Discontinuations due to AEs and SAEs
- Vital signs
- Laboratory test abnormalities

Look carefully for issues such as:
1. Liver injury
2. Bone marrow toxicity
3. Skin manifestations
4. QT prolongation
The CER Template (VI) – benefit / risk

- Assessment of benefits
  - Strengths and uncertainties
- Assessment of risks
  - Strengths and uncertainties
- Limitations of data
  - E.g. external validity of trial, use in real world
- Benefit / risk balance
- Recommendations regarding authorisation
- Recommendations regarding PI/CMI and RMP (safety specifications)
The CER Template (VII) – Product Information

• A Product Information document (PI) provides health professionals with a summary of the scientific information relevant to the safe and effective use of a prescription medicine.

• Wording is proposed by sponsor

• Needs evaluation
  – E.g. indications
    The therapeutic applications should be stated clearly and concisely, and should define the target disease or condition, distinguishing between treatment (symptomatic, curative or modifying the evolution or progression of the disease), prevention (primary or secondary) and diagnostic indications. Mandatory conditions of product usage, where relevant, should also be included if not covered more appropriately in other parts of the PI.
  – E.g. Precautions
  – E.g. dosage and administration

• Published on TGA website / new app
What makes a good Clinical Evaluation Report?

A good Clinical Evaluation Report is one that:

- uses the prescribed evaluation report template, is well written and has been proof-read prior to submission to the delegate;
- considers all the clinical data contained in the submission;
- contains an independent, objective and critical appraisal of the sponsor’s data, rather than simply summarising the data;
- refers to and applies relevant TGA guidelines;
- includes succinct summaries of the pharmacology, efficacy and safety of the product;
- has a well-argued balance of the benefits and risks of the product in relation to its proposed use;
- contains a clear set of recommendations regarding approval or otherwise of the application;
- includes a detailed review of the adequacy of the sponsor’s proposed Product Information and Consumer Medicine Information; and
- where necessary, contains clear questions to be asked of the sponsor to address any uncertainties about the clinical data package.

- Discuss if and why EU or FDA did not approve the medicine, or major differences in the PIs
- Highlighting discrepancies, gaps in reporting, safety or potential safety signals, missing data
- If recommending rejection - write the reasons clearly in dot points
- Ensure all Module 5 data is evaluated
- Your report is an independent assessment of the clinical data.
- We are very interested in your thorough assessment of the Product Information and CMI documents.
EU Guidelines

- The TGA closely aligns its regulatory approaches to therapeutic products with those of comparable international regulatory counterparts wherever possible.

- Technical data requirements for applications to register or vary the registration of prescription medicines in Australia are closely aligned with requirements set out in relevant European Union (EU) Guidelines and Guidelines issued by the International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use.

**Evaluation Timelines**

- Give yourself enough time – don’t leave it to the last minute!

- Know when the report is due back to the TGA – consider both Round 1 AND Round 2

- Allocate sufficient time to aspects such as: weighing benefit / risk; PI review; formatting / editing; etc

- Allow time to submit a draft report and receive feedback on it

- Round 1 is maximum 3 months

- Round 2 is maximum 1 month
Interaction with the TGA

Contact person from Clinical Evaluation Section – often the Delegate for the application

Support from External Evaluation team (e.g. IT issues)

If you have questions or just want to talk through an issue – talk to the delegate or member of the team

Feedback will be provided on your draft report, and changes may be required
Other resources

Resources that may be sent to you with the Dossier:
- EU Guidelines
- Overseas reports
- Previous TGA reports and advisory committee meeting outcomes – as identified by the Delegate

Other resources you may wish to use
- Publications
- Clinical guidelines (e.g. for evidence of standard of care)