INTRODUCTION

Therapeutic Goods Administration (TGA)

The TGA is the key division of the (Department of Health and Aged care) DHAC of commonwealth government of Australia concerned with the actual registration process. The TGA has an objective to ensure the safety, quality and efficacy of therapeutic goods available in Australia at a standard equal to that of comparable countries, and that pre-market assessment of therapeutic goods is conducted within a reasonable time.

The TGA is made up of six branches

- Drug Safety and Evaluation Branch (DSEB)
- Chemicals and Non-Prescription Drug (CNPD)
- Conformity Assessment
- TGA Laboratories
- TGA International Services
- Business and Services

Separate branches of the TGA are responsible for prescription drug evaluation, OTC drug evaluation, regulation of therapeutic devices and compliance issues.

The mechanisms used to ensure the quality; safety and efficacy of therapeutic goods are:

- pre-market assessment
- manufacturing controls
- post-market monitoring

Therapeutic Goods

A 'therapeutic good' is broadly defined as a good which is represented in any way to be, or is likely to be taken to be, for therapeutic use (unless specifically excluded or included under Section 7 of the Therapeutic Goods Act 1989). The principal legislation relevant to the supply of therapeutic goods used in Australia, whether manufactured in Australia or elsewhere, or exported from Australia is:

- Therapeutic Goods Act 1989 (the Act)
- Therapeutic Goods Regulations 1990 (the Regulations)

The Sponsor

The sponsor of a medicine is the person or company responsible for applying to the TGA to have their medicine included in the ARTG. Under the Act, a sponsor is someone who:

- imports therapeutic goods; or
- manufactures therapeutic goods; or
- has therapeutic goods imported or manufactured on their behalf, or
- Exports therapeutic goods from Australia.

Joint applications may be made where all or part of the data to support registration of the medicines is shared by two or more sponsors. In this circumstance, the parties jointly contributing the data are considered joint sponsors. In the case of joint applications, the product of each sponsor is separately entered onto the ARTG.
CATEGORIES OF APPLICATIONS FOR PRESCRIPTION ONLY MEDICINES

Category 1 applications
Category 1 applications include applications for a new chemical entity or a new indication for a registered prescription product as well as other major changes such as changes to product information or approval of a new generic medicine. Essentially, Category 1 catches applications not included in Category 2 or 3. For example, an application for a medicine containing a new active substance normally belongs to Category 1 or 2. Applications for new dosage forms, new strengths and new generic products are usually Category 1 applications. New chemical entities and substances and products are evaluated through the DSEB.

Category 2 applications
When an application has been previously approved in two acceptable countries these applications have a shorter statutory time frame for evaluation. For a Category 2 application, two independent evaluation reports from acceptable countries, where the product is already approved, are required to be provided at the time of application. The evaluation reports must be independent and the product proposed to be registered in Australia should be identical to that registered in the acceptable countries, with respect to formulation, directions for use and indications. Please note that if the data submitted in Australia are different to that submitted overseas, questions may be raised leading to a delay in approval. Any differences in the data submitted in the various countries should therefore, be clearly identified.

The countries currently identified by the Minister as acceptable, for the purposes of providing evaluation reports, are Canada, Sweden, the Netherlands, the United Kingdom and the United States of America.

Category 3 applications
Category 3 applications involve a change to a product that is already registered on the ARTG, where the change does not require quality data (clinical, toxicological or bioavailability data) to support the change.

THE TGA APPROVAL PROCESS
Before a prescription medicine can be supplied in Australia, it must be included in the Australian Register of Therapeutic Goods (ARTG). In order to register a new medicine in Australia a sponsor (usually a pharmaceutical company) must submit an application together with supporting data to the TGA. After an application is submitted, there is an initial period during which the application is assessed on an administrative level to make sure that the application complies with basic guidelines (the Application Entry Process; AEP). Prior to submission the file there should be pre-submission meetings. Currently, pre-submission meetings are not a regulatory requirement but are strongly encouraged by the TGA. Some of the issues that the TGA discusses with sponsors during pre-submission meetings include the availability of evaluation reports from other regulatory agencies, the possibility of negotiating shared evaluations, and drug specific issues. Such issues include:

Complex applications
A face-to-face meeting with TGA staff is appropriate for complex applications, especially if there is a need for either party to provide clarity on a particular issue or there is some uncertainty as to whether the registration dossier to be submitted will meet all Australian regulatory requirements.

Orphan drug applications
To register a medicine under the Orphan Drug Program, a sponsor must first seek orphan drug designation. Once orphan drug designation is
granted by TGA, the sponsor may submit an application for registration.

**Literature based submissions**

If the normal supporting data set is not available, the TGA will consider accepting literature based submissions for the purposes of updating the Product Information documents of medicines with an extensive registration history, either in Australia or overseas. Under exceptional circumstances, a literature based submission may be used for the registration of a new chemical entity in Australia where, although the product may not have been in the ARTG, it has been approved in other countries for many years. If the normal research-based data set is incomplete, applicants may supplement the data with literature-based data.

**Priority Evaluations**

The Director of DSEB may give priority evaluation status to a Category 1 or 2 applications. Requests for priority evaluation should be discussed at a pre-submission meeting and will be considered in circumstances where:

- the active ingredient is a new chemical entity; and
- the medicine is indicated for the treatment or diagnosis of a serious, life threatening or severely debilitating disease or condition; and
- There is clinical evidence that the medicine may provide an important therapeutic gain.

The allocation of priority evaluation status is not a guarantee that the total processing time of the application will be shortened, but the evaluation process will be performed as rapidly as possible.

**FDA Data Package**

Where registration is being sought for a new medicine to treat a life threatening illness or to treat a condition for which no satisfactory alternative therapy exists, the TGA may accept the application in the US version rather than the usual EU version of the CTD format. Sponsors who are considering the submission of an application in the US version must discuss the application, and the implications of any differences in format or content, with the TGA before submission.

**Additional Data**

Additional data are data, identified prior to the acceptance of an application, which the TGA agrees to accept during the course of the subsequent evaluation.

**Fixed Combination Submissions**

For a new fixed combination product the sponsor should justify the particular combination and the type and extent of data to be submitted.

**Submission of Applications**

Applications should be made using the appropriate DSEB Application Form. The DSEB requires the submission of all relevant quality data, non-clinical data, and clinical data to support the application. The original of the DSEB Application Form and a copy of the Sponsor’s application letter should be sent to the Financial Services Group (FSG) of the TGA with the appropriate evaluation fee payable.

**Submission of new data:**

For administrative purposes, new data submitted by the sponsor, after acceptance of the application for evaluation, are classified in terms of additional data and supplementary data. (Supplementary data are clinical or non-clinical data submitted at the initiation of the sponsor, which require evaluation and address any possible or perceived deficiencies identified in an Evaluation Report.) Additional data must be well defined and relate to a particular and limited aspect of the application. Acceptance of additional data for evaluation is at the discretion of the TGA and is not intended to facilitate inadequate or premature applications.
Any additional data are to be submitted to the TGA by a date mutually agreed between the TGA and the sponsor at a pre-submission meeting. No other data should be submitted during the evaluation of an application, other than relevant safety data and data specifically requested by the TGA.

**Application Acceptance:**

The Application Entry Team (AET) of the DSEB will conduct an administrative screen of the application before the dossier is accepted for evaluation to ensure that there are no deficiencies that would render the application un-evaluable. If any major deficiencies are found, further information will be sent to the sponsor. The acceptability of any confidentiality statement covering the application will be considered at this time. Any deficiencies identified must be addressed with the DSEB before the application can be accepted for evaluation. A screening fee is applicable if the submission is rejected at this point or withdrawn prior to acceptance.

Before the application can be accepted for evaluation, the appropriate evaluation fee must be received by the FSG. If the sponsor has paid insufficient fees, the FSG will invoice the sponsor for the outstanding amount that must be paid within 2 months.

Once the application is accepted for evaluation the sponsor will be sent a letter notifying data acceptability and the statutory evaluation period that will apply. This letter will include a TGA Identification Number (TGAIN) and a Submission Number. These numbers should be quoted in all subsequent correspondence related to the application.

**Tracking Applications**

The Submission Number should be used to track the progress of the application throughout the evaluation process by using the TGA’s tracking system (Premier) via the Internet.

**Provisional ARTG numbers:**

A Provisional ARTG number will be allocated soon after an application is received by DSEB. When the product is registered, the Provisional ARTG number will become the AUST R number, which is included on the packaging. The Provisional ARTG number will allow sponsors to develop the packaging and labeling artwork for their product in preparation for registration.

**Evaluation:**

**External evaluators:**

The TGA may contract external evaluators to review aspects of the data. A TGA Delegate will coordinate the evaluation with the external evaluator. Communication with the sponsor in relation to an evaluation will be through the TGA Delegate. The identity of external evaluators is generally kept confidential. Under Section 31 of the Act, the TGA may request information additional to that provided in the dossier, or may seek clarification of information provided. Such requests are referred to as Section 31 requests. For an application, these requests may be issued at any time from submission of the application to marketing approval. The evaluation clock is stopped until a full response to the S31 request is submitted. All Section 31 (S31) requests are identified with a unique identification number, a S31 Request Number. This number should be quoted in the heading of any response to the request. S31 requests should be answered in full and within the timeframe stipulated in the letter of request. Should a sponsor anticipate difficulty in answering a S31 request in full or within the specified timeframe, they should contact the signatory of the letter to discuss the request as soon after receipt as possible. If a sponsor considers that
a S31 request is unreasonable they should discuss this with the Delegate who issued the request. If the sponsor is not satisfied with the outcome of the discussion, the sponsor may request a review of the issue by the Standing Arbitration Committee (SAC) or Pharmaceutical Sub-Committee (PSC).

Section 31 requests regarding a closed part of a Drug Master File (DMF) or Plasma Master File (PMF) will be sent by TGA directly to the manufacturer concerned. The TGA will notify the sponsor that this request has been made.16,17

**Processing Times**

The time taken for the sponsor to respond to Section 31 requests is excluded from the processing times; the time allowed for evaluation of the application will be extended by the time taken to respond fully to the request. Partial responses to a Section 31 request will not restart the evaluation clock. Also, should a response not contain the S31 Request Number, the evaluation clock will not restart until 5 working days after receipt of the sponsor's response to allow for matching the response with the original request.3

**Table 1:** Timeframes for the application entry process

<table>
<thead>
<tr>
<th>Category</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category 1</td>
<td>40 working Days</td>
</tr>
<tr>
<td>Category 2</td>
<td>20 working Days</td>
</tr>
<tr>
<td>Category 3</td>
<td>5 working Days</td>
</tr>
</tbody>
</table>

If an evaluation has not been completed within specified time for Category 1 and 2 applications, the sponsor may notify the Secretary in writing that the sponsor wishes to treat the application as having been refused. The sponsor may then proceed with a request for reconsideration. Formal timeframes have not been established for priority evaluations.3 Although there is no statutory processing time associated with notification of self-assessable changes, the TGA will acknowledge receipt of the notification. The TGA may at any time, following acknowledgement of the change, contact the Sponsor to request relevant validation data for review.

**Table 2:** The legislated timeframes for assessment of applications:

<table>
<thead>
<tr>
<th>Category</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category 1</td>
<td>Within 255 working Days</td>
</tr>
<tr>
<td>Category 2</td>
<td>Within 175 working Days</td>
</tr>
<tr>
<td>Category 3</td>
<td>Within 45 working Days</td>
</tr>
</tbody>
</table>

Where self-assessable changes require notification, the TGA also requires that a date of implementation be advised.

**Table 3:** The time taken for different types of applications:

<table>
<thead>
<tr>
<th>Category</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>New Chemical Entities</td>
<td>Within 150 working Days</td>
</tr>
<tr>
<td>New Generics</td>
<td>Within 100 working Days</td>
</tr>
<tr>
<td>New Indications</td>
<td>Within 160 working Days</td>
</tr>
<tr>
<td>Product Information Changes</td>
<td>Within 90 working Days</td>
</tr>
<tr>
<td>Additional Trade Names only</td>
<td>Within 45 working Days</td>
</tr>
</tbody>
</table>

**Fees:**

Fees will vary according to the type of evaluation undertaken and are on a per submission basis.

**Table 4:** Fees and charges for evaluation:

<table>
<thead>
<tr>
<th>Category</th>
<th>Fee $</th>
</tr>
</thead>
<tbody>
<tr>
<td>New Chemical Entities</td>
<td>170,200</td>
</tr>
<tr>
<td>New Generics</td>
<td>65,000</td>
</tr>
<tr>
<td>New Indications</td>
<td>101,200</td>
</tr>
<tr>
<td>Product Information Changes</td>
<td>65,900</td>
</tr>
<tr>
<td>Additional Trade Names only</td>
<td>10,700</td>
</tr>
</tbody>
</table>
Overseas rejections and withdrawals during evaluation:

Sponsors should notify the TGA of overseas rejections and withdrawals of applications and significant regulatory actions. Sponsors should also notify the TGA of any serious adverse reactions which are observed for the first time or are inconsistent with that reported in the application.

Withdrawal of Applications:

A sponsor may withdraw an application at any time following submission up until the Delegate's decision on the application is made. If the evaluation is substantially complete at the time the application is withdrawn, that is, the Module 3, 4 and 5 Evaluation Reports have been completed; the remaining 25% of the evaluation fee must be paid by the sponsor. The TGA may retain the data and any other material submitted in connection with the Application. Where an application is withdrawn due to safety concerns the sponsor may be asked to provide any adverse safety data in its possession to the TGA.

Evaluation Reports:

Each DSEB Evaluation Section provides the sponsor with an edited copy of their evaluation report, except for Category 3 and minor Category 1 applications. Where the DSEB refers an application to ADEC (Australian Drug Evaluation Committee) for advice, these reports are also provided to ADEC. The evaluation reports are forwarded to the sponsor as soon as they have been accepted by DSEB. The sponsor should review these reports and advise the TGA of any perceived errors of fact or major omissions in the evaluation reports. The sponsor should also amend the texts of the proposed PI to the extent the applicant sees fit. This allows for concerns to be addressed early and contributes to shorter post-ADEC negotiations, leading to earlier approval.

Supplementary Data:

Supplementary data may be submitted after a sponsor has received either or both of the non-clinical data and clinical data Evaluation Reports. The sponsor must notify their intention to submit supplementary data within 5 working days of receipt of the last Evaluation Report. Only one submission of supplementary data will be permitted for each of non-clinical data and clinical data, unless otherwise agreed in writing by the Delegate. Supplementary data will not be accepted after commencement of the pre-ADEC process, which is signified by the issuing of the Delegate’s Request for ADEC Advice and recommendation. Acceptance of supplementary data is at the discretion of the TGA and is dependent upon mutual agreement to a clock stop:

- up to 60 working days will be allowed for all data to be presented to the TGA following the sponsor’s notification of an intention to submit supplementary data; and
- Up to 135 days will be taken for evaluation of the supplementary data after all data have been received by TGA Delegate’s request for ADEC advice:

At the completion of evaluation by the DSEB, an application may be referred to ADEC for advice. The DSEB is not obliged to refer applications to ADEC but generally does so for major applications. Examples of where ADEC may not be consulted could include positive decisions for new generics or orphan Drugs. There are also abridged processes that may be used on occasions (ADEC reference panel). After evaluation of the application, the TGA Delegate will review the evaluation reports and prepare a Request for ADEC Advice, if relevant. The Delegate's Request identifies the issues of importance concerning the application, including proposed recommendations to approve or reject the
application. A copy of the Request is sent to the sponsor. The Request for ADEC Advice is intended for review by ADEC.

**Pre-ADEC phase**

Prior to referral to ADEC, the sponsor has an opportunity to respond to the Delegate’s Request for ADEC Advice and proposed recommendation. The sponsor has a minimum of 10 working days following receipt of the Delegate’s Request for ADEC Advice to provide a response and to submit any additional comment on the application. Sponsors may be given the opportunity to have a shortened pre-ADEC consultation period if this allows a medicine to go to an earlier ADEC meeting. This is only done by mutual consent.

The sponsor’s Category 1 application letter, all evaluation reports, the Request for ADEC Advice (including a proposed recommendation), and the sponsor’s pre-ADEC response are submitted to ADEC for consideration.

The sponsor’s pre-ADEC response:

- should be printed in 12-point font and should be no longer than six A4 pages
- All pages of the response should be numbered and
- No documents should be appended to it, other than the standard appendices outlined below or other information specifically requested by the TGA.
- The presentation of the pre-ADEC response should be simple (unbound, unstapled) in order to allow easy replication of all pages.
- Two copies of the pre-ADEC response are required.

The sponsor’s pre-ADEC response should include the following appendices:

- A tabulation of any serious unexpected adverse drug reactions which are not mentioned in the proposed Australian PI\(^2\) and have not been submitted previously
- it is expected that this would normally not exceed six pages;
- An updated proposed Australian PI and the most up-to-date Consumer Medicine Information (CMI). Highlight changes from the version submitted with the application and reference the source of the change (for example, clinical evaluation, company base document) in the margin.
- The Adverse Reactions section of the PI should be presented in the CIOMS format (Report of CIOMS Working Group III).
- a statement of the current international regulatory status of the drug. This should detail approvals (with indications), deferrals, withdrawals and rejections (with reasons for the last three);
- the US Product Information, Canadian Product Monograph, the UK Summary of Product Characteristics (SmPC) and an English translation of the Swedish SmPC, where available;

The pre-ADEC response should also include a copy of the latest Periodic Safety Update Report (PSUR), unless already supplied or not available.\(^3\)

**Post-ADEC (Decision phase)**

After receipt of the ADEC Resolution, the Secretary or his/her Delegate (the TGA Delegate) will decide whether the application for registration is to be approved or rejected. The sponsor will be advised of the decision of the Secretary or the Delegate within 28 days of the decision being made. This is referred to as an initial decision. If the TGA Delegate proposes to approve the application, he/she will communicate with the sponsor to address any outstanding issues relating to the
application. At this stage the final PI and CMI will be negotiated between the TGA and the sponsor. If a Delegate proposes to reject an application, a letter of decision will be sent to the sponsor. The letter will contain the reasons for the decision and set out the appeal rights. A formal statement of reasons may be requested from a Delegate. In cases where an ADEC proposal to reject an application is unexpected, for example, contrary to the Delegate’s pre-ADEC intentions, the Delegate will usually contact the sponsor to discuss the proposed actions. A sponsor may appeal the decision of a Delegate.

Post-Approval Procedures
Upon approval of a new register entry, the sponsor will be sent a Certificate of Registration with a unique AUST R number. The annual registration charge is payable following registration. The sponsor should notify the TGA of the actual date of commencement of marketing. The provisional ARTG record will have already been checked during the quality evaluation process and will become the ARTG Record of Registration.

Scheduling
After a product containing a new medicine has been evaluated by the DSEB and considered by ADEC, the evaluation outcomes are provided to the National Drugs and Poisons Schedule Committee (NDPSC). The NDPSC determine the appropriate schedule for the new chemical entity. Sponsors do not need to apply for a schedule for a new medicine as this is managed by the TGA during the registration process. However, if a sponsor wishes to seek an alternative schedule entry for a new medicine, then an application must be made to the NDPSC with suitable evidence to support the schedule entry proposed.

- Prescription-Only Medicine comes under schedule 4
- Medicines which are available with the prescription of a doctor, dentist or veterinarian
- In general, all new chemical entities or compounds not previously available in Australia are first classified as prescription-only medicines.

Appeal Provisions:
The Act provides a comprehensive system for review of administrative decisions. Sponsors should also consider the informal avenues of appeal.

Informal appeal mechanisms:
Requests for review can be made to the Standing Arbitration Committee for Therapeutic Goods (SAC) or the Pharmaceutical Sub-Committee (PSC) of ADEC during an evaluation.

Formal appeal mechanisms:
Section 60 Appeals – Decisions by the Secretary or a delegate of the Secretary that are subject to review may be appealed under Section 60 of the Act. Examples include:

- a refusal to register or list goods on the ARTG,
- the variation or addition of conditions applying to a registration or listing,
- cancellation of a registration or a listing, or
- Revocation or suspension of a manufacturing licence.

If a decision is appealable, the decision letter will usually include details of appeal rights in the letter of decisions. Except as described below regarding deemed refusals, an appeal to the Minister must, in the first instance, be made within the time limit of 90 calendar days of notification of the original decision. The appeal letter should be sent to the Parliamentary Secretary of the Minister for Health and Ageing Parliament House, Canberra ACT 2600 and should be clearly marked Appeal under Section 60 of the Therapeutic Goods Act 1989. A copy of
the letter should be sent to the TGA National Manager.

The Minister, or the Minister’s delegate for this purpose, may confirm or revoke the initial decision or substitute a new decision. If a sponsor has not received a response from the Minister or the Minister’s delegate within 60 calendar days of receipt of the appeal, the first decision is deemed to be upheld.

If a sponsor wishes to appeal but is unable to do so before the 90 day deadline, then the sponsor should contact the TGA Information Officer. Extensions of time are only given in exceptional circumstances. Details of the reason for the inability to lodge the appeal in the specified time should be provided in writing.3

**Administrative Appeals Tribunal:**
If not satisfied with the outcome of a Section 60 appeal, the appellant may apply to the Administrative Appeals Tribunal (AAT) for review. Applications to the AAT must be made within 28 calendar days of the Minister’s decision following reconsideration. The AAT may affirm the decision, vary it or set it aside, substitute a new decision, or refer the decision back to the original decision maker.3

**Federal Court:**
Whereas the AAT provides a merit review process, affected parties may appeal, on the grounds of the legality of a decision, to the Federal court at any time.3

**Deemed Refusal:**
A deemed refusal may apply where the TGA has failed to complete a Category 1 or 2 evaluation within the specified evaluation time. In this case the sponsor may write to the Secretary and advise that the application should be treated as having been refused. This constitutes a deemed refusal of the Secretary and the sponsor may then appeal for review of this refusal.3

**GENERAL ADMINISTRATIVE REQUIREMENTS**

The documentation to support a registration application should be compiled in accordance with the current version of *The Rules Governing Medicinal Products in the European Union* Volumes 2B (2003 CTD version). Please note that the EU CTD modules 3-5 have been adopted without their annexes (which are lists of Guidelines currently "in force" in Europe). For a list of EU/ICH guidelines adopted in Australia. Additional Australian administrative requirements are described in Module 1.

The additional Australian technical guidance concerning the chemical, quality and biological documentation, the non-clinical documentation and clinical documentation, which are provided in appendices to this document, should also be taken into account when preparing the application dossier.

**Multiple applications with common data:**
In general a separate application for registration is required for each separate and distinct therapeutic good. If applications for registration of several products containing the same active ingredients are submitted at the same time, relevant documentation may usually be submitted in a combined form. Fees are charged per submission. A submission is one or more applications from the same sponsor, with the same active ingredient, submitted at the same time. A concomitant application from, or on behalf of, another sponsor is a separate submission. The Secretary may also provide for several separate goods to share a single registration number in a process called grouping. The characteristics that determine a separate and distinct good under the Act are listed under Subsection 16(1) of the Act. Determinations...
on the grouping of otherwise separate and distinct medicines may be found in the Therapeutic Goods (Groups) Order No. 1 of 2001.

Where should be applications sent? Applications and fees should be submitted to the TGA as follows:

To the Financial Services Group:
For a Category 1 or 2 application send:
- A DSEB Application Form;
- A copy of the letter of application;
- 75% of the relevant evaluation fee (this is optional if the fee is greater than $100,000).

To the Drug Safety Evaluation Branch
For a Category 1 or 2 application send:
- A letter of application setting out the reasons for the application
- Administrative information, including a completed DSEB Application Form (Module I);
- Documentation (data) supporting the application (Modules 2-5).

For a notification (including safety-related notifications) send:
- A letter outlining the reasons for the notification;
- A completed DSEB Notification Form for notification of self-assessable changes to the quality information, if required;
- The processing fee;
- Any relevant attachments.

REFERENCES