



**Australian Government**

**Department of Health and Ageing**  
Therapeutic Goods Administration

# Australian regulatory guidelines for prescription medicines (ARGPM)

June 2004

**TGA** Health Safety  
Regulation



## About the Therapeutic Goods Administration (TGA)

- The TGA is a division of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- TGA administers the Therapeutic Goods Act 1989 (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website.

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Historical document

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# Abbreviations and acronyms

AAN	Australian Approved Name
AAT	Administrative Appeals Tribunal
ADEC	Australian Drug Evaluation Committee
ADRAC	Adverse Drug Reactions Advisory Committee
ADRU	Adverse Drug Reactions Unit (TGA)
AET	Application Entry Team (TGA)
API	Active Pharmaceutical Ingredient
AQIS	Australian Quarantine Inspection Service
ARGPM	Australian Regulatory Guidelines for Prescription Medicines
ARGOM	Australian Regulatory Guidelines for OTC Medicines
ARPANSA	Australian Radiation Protection and Nuclear Safety Agency
ARTG	Australian Register of Therapeutic Goods (the Register)
AUST R	Australian Registration Number (for prescription medicines)
BP	British Pharmacopoeia
CAS	Chemical Abstract Services
CEP	Certificate of Suitability (Ph Eur monograph)
CHMP	Committee for Medicinal Products for Human Use (formally Committee for Proprietary Medicinal Products) (EU)
CI	Colour Index
CIOMS	Council for International Organisations of Medical Sciences
CMEC	Complementary Medicines Evaluation Committee
CMI	Consumer Medicine Information
CPD	Certified Product Details
C(PI) Regs.	Customs (Prohibited Import) Regulations
CTD	Common Technical Document
DMF	Drug Master File
DSEB	Drug Safety & Evaluation Branch (TGA)
EDQM	European Directorate for the Quality of Medicines
EMA	European Medicines Agency (formally the European Agency for the Evaluation of Medicinal Products) (EU)

EU	European Union
EudraLex	The Rules Governing Medicinal Products in the European Union
FDA	Food and Drug Administration (United States)
FFS	Form Fill Seal
FOI	Freedom of Information
FSANZ	Food Standards Australia New Zealand
FSG	Financial Services Group (TGA)
GC	Gas Chromatography
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMO	Genetically Modified Organism
GMP	Good Manufacturing Practice
GTRAP	Gene and Related Therapies Research Advisory Panel
HPLC	High Performance Liquid Chromatography
HREC	Human Research Ethics Committee
ICH	International Conference on Harmonisation (of Technical Requirements for Registration of Pharmaceuticals for Human Use)
ICRP	International Commission on Radiological Protection
INS	International Numbering System (for food additives)
IPD	Individual Patient Data
IR	Infra Red
JECFA	Joint FAO/WHO Expert Committee on Food Additives
JETACAR	Joint Expert Technical Advisory Committee on Antibiotic Resistance
LAL	Limulus amoebocyte lysate
MAS	Manufacturers Assessment Section (TGA)
MEB	Medicines Evaluation Board (The Netherlands)
MEC	Medicines Evaluation Committee
MHPRA	Medicines and Healthcare Products Regulatory Agency (UK)
MoU	Memorandum of Understanding
MPA	Medical Products Agency (Sweden)
NCE	New Chemical Entity
NDPSC	National Drugs and Poisons Schedule Committee
NHMRC	National Health and Medical Research Council
NIR	Near Infra Red
NPMB	Non Prescription Medicines Branch (TGA)
NTA	Notice to Applicants (EU)

OECD	Organisation for Economic Co-operation and Development
OGTR	Office of the Gene Technology Regulator
PAR	Provisional ARTG Record
PBAC	Pharmaceutical Benefits Advisory Committee
PBS	Pharmaceutical Benefits Scheme
PCES	Pharmaceutical Chemistry Evaluation Section (TGA)
PCTFE	Polychlorotrifluoroethylene
pdf	Portable document format
Ph Eur	European Pharmacopoeia
PD	Pharmacodynamics
PI	Product Information
PK	Pharmacokinetics
PMF	Plasma Master File
PSC	Pharmaceutical Sub-Committee (ADEC)
PSUR	Periodic Safety Update Report
PVC	Polyvinylchloride
PVDC	Polyvinylidene chloride
qc	Quality Control
SAN	Self-Assessment Notification
SAC	Standing Arbitration Committee (for Therapeutic Goods)
SECTSE	Special Expert Committee on Transmissible Spongiform Encephalopathies (NHMRC).
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics (European)
SRN	Safety Related Notification
SUSDP	Standard for the Uniform Scheduling of Drugs and Poisons
TGA	Therapeutic Goods Administration
TGAL	TGA Laboratories Branch
TGAIN	TGA Identification Number
TGO	Therapeutic Goods Order
TPD	Therapeutic Products Directorate (Canada)
TSE	Transmissible Spongiform Encephalopathies
UK	United Kingdom
US	United States of America
USP	United States Pharmacopeia

# 1. Introduction

These guidelines will assist sponsors to prepare applications to register new prescription or other high risk medicines for human use in Australia, or to vary existing medicine registrations. The format for applications is the Common Technical Document (CTD)<sup>1</sup>. These guidelines are not intended to replace the CTD guidelines but to provide explanation that complements the CTD. These are guidelines, and not legally binding.

In order to be imported into, manufactured in, supplied in or exported from Australia, medicines must be included in the Australian Register of Therapeutic Goods (ARTG, the Register). Intending sponsors of medicines must apply to the Therapeutic Goods Administration (TGA) for the inclusion of their product on the Register.

## 1.1 Scope of these guidelines

These guidelines describe the information to be supplied with an application to include a new medicine in the ARTG. They apply to medicines that are evaluated by the Drug Safety and Evaluation Branch (DSEB) of the TGA, in accordance with Section 25 of the *Therapeutic Goods Act 1989*. All prescription medicines and certain other high-risk medicines such as injections (see Section 2.3) come under this category.

The guidelines also describe the information to be submitted with applications to vary information about these medicines.

The TGA has adopted the CTD format for the documentation of data on the quality<sup>2</sup>, non-clinical<sup>2</sup> and clinical aspects of medicines. Further explanation of the Australian requirements is provided either in the appendices to this document or an Internet location is identified.

Requirements may vary when an application is for the registration of a product that does not contain a new active ingredient. Section 4 of these guidelines provides guidance on the modified requirement in these circumstances.

The Australian general administrative requirements are described in Section 5 of this document. Sponsors should check the TGA website for the latest version of these guidelines and not rely on printed copies routinely.

Guidelines on the registration or listing of other types of therapeutic goods are available from the TGA Information Officer.

## 1.2 References in the guidelines

Where information referenced in this document has been published as a separate document, this is indicated in the guidelines and a reference is given for the location of the document.

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<sup>1</sup> <http://www.tga.gov.au/industry/pm-ctd.htm>

<sup>2</sup> In these guidelines the term quality is used to describe chemical, pharmaceutical and biological studies, the term non-clinical is used to describe preclinical, pharmaco-toxicological and pharmacological/or toxicological studies.

## 1.3 Legislation applying to the supply of therapeutic goods

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)*<sup>3</sup>
- *Therapeutic Goods Regulations 1990 (the Regulations)*<sup>3</sup>

The annual charges for the registration and listing of therapeutic goods and for the licensing of manufacturers are set out in:

- *Therapeutic Goods (Charges) Act 1989*<sup>3</sup>
- *Therapeutic Goods (Charges) Regulations 1990*<sup>3</sup>.

The TGA, a Division of the Australian Department of Health and Ageing, is responsible for the administration of all of the above legislation.

## 1.4 Import permits and quarantine clearance

Under the *Customs (Prohibited Imports) Regulations*, importers of narcotics, psychotropic medicines, anabolic steroids, growth hormones, antibiotics and radioactive substances must obtain an import permit and/or licence. An application for a licence to import should be made in writing to the Head, Treaties and Monitoring Section, TGA. Licences are issued subject to Regulation 5 of the *Customs (Prohibited Imports) Regulations* by an authorised person from the TGA. Information on which goods require a permit and how to apply for a permit is available on the TGA web site. Customs requirements can vary and it is the responsibility of the sponsor to keep abreast of requirements in relation to goods to be imported.

Importers of biological products are also advised to obtain clearance from the Australian Quarantine and Inspection Service (AQIS).

Legislation applicable to the importation and exportation of medicines into Australia includes:

- *Customs Act 1901*<sup>4</sup>
- *Customs (Prohibited Imports) Regulations* (relevant to narcotics, psychotropic medicines, anabolic steroids, growth hormones, antibiotics, radioactive substances and other medicines specified by Customs Regulations/Orders)<sup>4</sup>
- *Quarantine Act 1908* (materials of biological origin)<sup>4</sup>
- *Customs (Prohibited Exports) Regulations*.

Additional legislation that may be relevant to the importation or supply of medicines in Australia includes:

- *Gene Technology Act 2000*<sup>4</sup>

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<sup>3</sup> <http://www.tga.gov.au/industry/legislation.htm>

<sup>4</sup> <http://www.comlaw.gov.au>

- *Gene Technology Regulations 2001*<sup>4</sup>
- *Wildlife Protection (Regulation of Imports and Exports) Act 1982*<sup>4</sup>
- *Trade Practices Act 1974*<sup>4</sup>
- *Commerce (Trade Descriptions) Act 1905*<sup>4</sup>
- State and Territory legislative requirements relating to labelling and scheduling.

## 1.5 Official standards for therapeutic goods

All medicines must comply with legislative requirements in force in Australia. Statutory Standards under the Act include the Therapeutic Goods Orders (TGOs) determined under the Act and the British Pharmacopoeia (BP)<sup>5</sup>. Where no standard is specified in a TGO or the BP, or where a sponsor is able to demonstrate that the safety and quality of a product will not be compromised, the TGA may allow that the product meet either a standard specified by another pharmacopoeia, such as the United States Pharmacopoeia (USP) or an agreed non-pharmacopoeial standard. Current TGOs are available from the TGA website<sup>6</sup>.

Under Section 14 of the Act, sponsors may seek an exemption from the requirement to conform with applicable standards for therapeutic goods imported into, supplied in or exported from Australia. Where an exemption from compliance with standards is granted by the TGA, conditions may apply (see Section 2.5.5).

## 1.6 Guidelines

The technical data requirements for the registration of medicines evaluated by the DSEB have been closely aligned with those required for applications for marketing authorisation of a medicine published by the European Union (EU). A list of EU guidelines adopted in Australia is available from the TGA website. For some EU guidelines adopted in Australia the TGA provides additional comments. These comments are noted on the TGA website listing of adopted EU guidelines.

Sponsors should consult the following guidelines in relation to the administrative and formatting requirements for applications:

- *Module 1: Administrative Information and Prescribing Information For Australia*<sup>7</sup>; and
- *Volume 2B: Notice to Applicants: Medicinal products for human use. Presentation and format of the dossier CTD* (July 2003)<sup>8</sup>

The specific Australian administrative requirements for registration applications are described in Module 1 of the Common Technical Document (CTD) published on the TGA website.

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<sup>5</sup> Where EC guidelines refer to the 'Pharmacopoeia of a Member State', in Australia this is taken to be a reference to the British Pharmacopoeia

<sup>6</sup> <http://www.tga.gov.au/industry/legislation-tgo.htm>

<sup>7</sup> <http://www.tga.gov.au/pdf/euguide/tgamod1.pdf>

<sup>8</sup> <http://pharmacos.eudra.org/F2/eudralex/vol-2/B/ctd2003july.pdf>

Sponsors should maintain an up to date knowledge of EU guidelines adopted by the TGA. Additions and revisions of the EU guidelines may be adopted in Australia. When a new guideline or revision is adopted in the EU, it is assessed by the TGA in consultation with the Australian pharmaceutical industry, to determine if it should be adopted in Australia. This assessment includes whether or not current guidelines need to be updated or replaced. The assessment outcome is published on the TGA website and in the *TGA News*.

All EU guidelines can be obtained from the European Medicines Agency (EMA) website<sup>9</sup>.

## 1.7 Implications of guidelines in Australia

In Australia, as in the European Union, guidelines are used as guidance for applicants. The EU use of guidelines as the basis for guidance for applicants is stated as:

*The use of guidelines, which are not legally binding, rather than a formal legal instrument, such as a Directive, has been preferred in order to maintain an element of flexibility and not place legislative restraints on scientific progress. It is recognised that in some cases, as a result of scientific developments, an alternative approach may be appropriate. However, where an applicant chooses not to apply a guideline, that decision must be explained and justified in the Expert Reports submitted by the company in support of the application.*

The Australian approach to guidelines is somewhat more flexible in the sense that other reasons, beyond scientific development, may be accepted as a rationale for a sponsor not to follow the guidelines rigidly. In Australia, situations such as the following may be relevant:

- a circumstance unique to the product in question can be demonstrated;
- a general guideline is not relevant in a particular instance;
- the sponsor adopts an acceptable approach which had not previously been considered by the TGA; or
- sufficient alternative studies have been conducted which, whilst not exactly what the guidelines seek, nevertheless satisfy the criteria of quality, safety and efficacy.

A sponsor has the option to argue that a particular guideline, or an aspect of a guideline, is not applicable to a given product. However, where sponsors opt to provide data that do not conform with the guideline, a justification should be provided explaining why the proposed alternative is valid.

Administrative guidelines, on the other hand, are in general applied less flexibly. Examples include the number of copies of documentation to be submitted, forms to be completed for administrative purposes, and the presentation of the dossier (see Section 5: *General Administrative Requirements*).

The flexible interpretation of guidelines does not apply to those circumstances where changes by self-assessment or notification under certain conditions are allowed, for example, *Changes to the Quality Information of Registered Medicines: Notification, Self-Assessment and Prior Approval* (Section 4.4.3 and Appendix 12) and *Safety-related changes to the Product Information* (Section 4.4.5.1). If there is any doubt in relation to the applicability of these guidelines, the sponsor should contact the TGA before making the change as unauthorised changes can attract penalties.

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<sup>9</sup> <http://www.emea.eu.int/index/indexh1.htm>

## 2. General overview

### 2.1 Who should apply?

All therapeutic goods must be included in the ARTG before they can be imported into, supplied in Australia or exported, unless they are exempt or excluded goods. Details of exemptions and exclusions are contained in the legislation. Sponsors of therapeutic goods are responsible for applying to the TGA to have their goods included in the ARTG. If there is any doubt as to whether a product is exempt or not, the TGA should be contacted for advice. A TGA contact list is available on the TGA website<sup>10</sup>.

There are special arrangements in place to allow supply of unapproved medicines in certain circumstances. For further details see the TGA Website.

#### 2.1.1 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. The sponsor must be a resident of Australia or be an incorporated body in Australia and conducting business in Australia.

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*.

However, for each product entry in the Register there can be only one sponsor. In the case of joint applications, the product of each sponsor is separately entered onto the ARTG. That is, the relationship of a product to a sponsor is one to one, but the relationship of a sponsor to products may be one to many (see also Section 4.1.2: *Confidentiality and freedom of information*).

### 2.2 Goods required to be included in the ARTG

All therapeutic goods must be included in the ARTG before they can be imported into, supplied in Australia or exported, unless they are exempted from inclusion on the Register under Section 18 or 19 of the Act or excluded by determination.

Medicines included in the ARTG are divided into two categories: registered goods or listed goods.

There are other categories of therapeutic goods, including medical devices and Australian Devices. The guideline *Device and Drug Distinctions*, available on the TGA website<sup>13</sup> should assist sponsors

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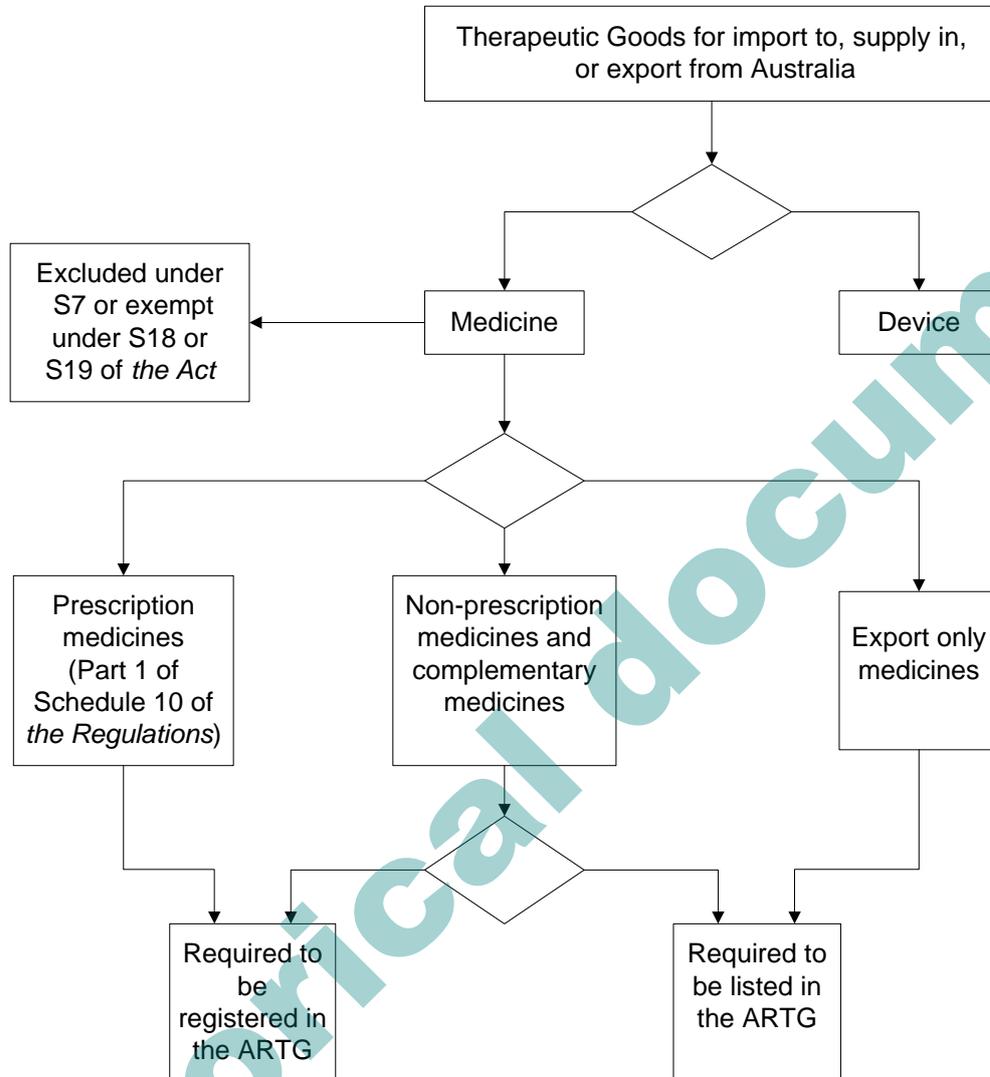
<sup>10</sup> <http://www.tga.gov.au/about/contact.htm>

to classify therapeutic goods not readily identified as medicines or devices. If there is any doubt TGA can be contacted.

Due to the broad definition of a *therapeutic good* some products (mostly therapeutic devices, rather than medicines) may be unintentionally included in the definition of a *therapeutic good* in the Act. In this circumstance, the goods may be granted a specific exclusion under Section 7 of the Act. An example of an excluded good is unmedicated soap. The description of these products is included in the Excluded Goods Order.

The Regulations describe which goods are in the registered, listed and exempt categories (see Figure 1).

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**Figure 1**Goods required to be included in the artg<sup>11</sup>

<sup>11</sup> For devices see the TGA website for further guidance:  
<http://www.tga.gov.au/docs/html/devguid9.htm>

## 2.3 Medicines required to be registered and evaluated by DSEB

Registered medicines are divided into two categories for assessment that can be broadly described as:

- *Prescription medicines* and some other special types of medicines regulated by the DSEB (Part 1 of Schedule 10 of the Regulations); and
- *Non-prescription medicines (Over-the-counter medicines)* and Complementary Medicines regulated by the Non-prescription Medicines Branch or the Office of Complementary Medicines.

The DSEB coordinates the evaluation of applications for registration, or variation to an existing registration, of therapeutic goods specified in Part 1 of Schedule 10 of the Regulations. These goods are:

- therapeutic goods containing a substance mentioned in Schedule 4, 8 or 9 to the Poisons Standard, or which meets the criteria for mention in any of those Schedules;
- a medical gas;
- a vaccine;
- an allergen, except an allergen for skin patch testing on unbroken skin;
- a biotechnology medicine;
- an immunoglobulin;
- a radiocontrast agent, except barium sulfate for radiological use;
- a radiopharmaceutical;
- a dialysis solution, except a haemodialysis solution;
- a special dosage form, such as a transdermal system and osmotic pump;
- an injectable medicine dosage form;
- a blood product, unless coated on a therapeutic device;
- goods referred to the DSEB for evaluation;
- an excipient in therapeutic goods mentioned in this part;
- a therapeutic device that depends upon the release of a substance for some or all of its action.

The ARGPM applies to medicines evaluated by the DSEB.

## 2.4 Justification for a particular route of evaluation

Schedule 10 to the Regulations also provides for applications to be referred between the different evaluation areas of the TGA. Usually, new chemical entities and substances and products included in Schedule 4, 8 or 9 of the *Standard for the Uniform Scheduling of Drugs and Poisons* (SUSDP) are evaluated through the DSEB. However, where a sponsor considers that a product or medicine does

not meet the criteria for inclusion in Schedule 4, 8 or 9 of SUSDP (*Guidelines for the National Drugs and Poisons Schedule Committee*<sup>12</sup>), the sponsor may apply to have the evaluation conducted via the Office of Complementary Medicines or the Non-Prescription Medicines Branch. The sponsor must provide a justification for an evaluation by the non-prescription medicine route prior to the submission of their application for registration or listing. This should be submitted to the branch heads of both branches (see Appendix 3 - *Justification for a Particular Route of Evaluation*).

Evaluation by the non-prescription route will only proceed where the sponsor has satisfied the TGA that the product or medicine does not meet the criteria for inclusion in Schedule 4, 8 or 9 of the SUSDP.

A flowchart of the overall regulatory framework for applications considered by DSEB is shown in Figure 2. This is a simplified flow chart and does not replace the detailed information in the reference sections of the text. Regulatory decisions should not be based solely on this flow chart.

## 2.5 Categories of applications

Therapeutic Goods Regulations 16A to 16G set out the conditions and statutory processing times relevant to each category (see also Section 3.5).

### 2.5.1 Category 1 applications

Category 1 applications are provided for under subregulations 16C(3)(b) and 16D(3)(b). An application for a new medicine or a change to a medicine constitutes a Category 1 application if it does not meet the specific requirements for 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. Extensions of indications and amendments to the Product Information (PI) are also normally Category 1 applications (see Section 4.1).

### 2.5.2 Category 2 applications

Category 2 application provisions can only be utilised when an application has been previously approved in two *acceptable countries*. Category 2 applications are provided for under subregulations 16C(3)(a) and 16D(3)(a). These applications have a shorter statutory time frame for evaluation. Further details are provided in Section 3.5.

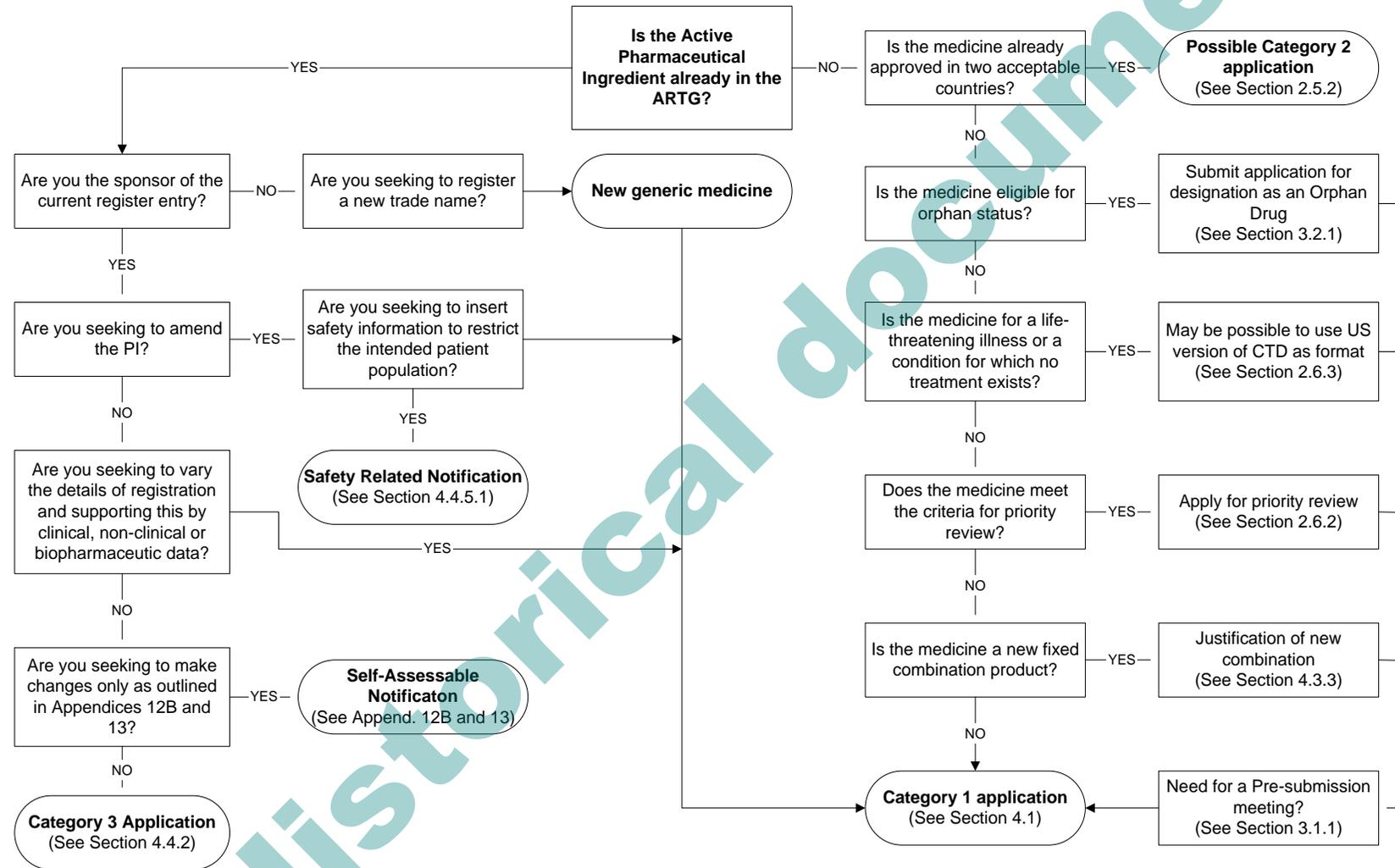
For a Category 2 application, two independent evaluation reports from *acceptable countries*, where the product is already approved, are required to be provided at the time of application. The evaluation reports must be independent (as described in subregulations 16C(4) and (5) and 16D(4) and (5)) and 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 (see Sections 4.1.6 and 4.2).

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<sup>12</sup> <http://www.tga.gov.au/ndpsc/ndpsc.htm>

**Figure 2**

Overall regulatory framework for medicines considered by DSEB



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. Any additions to these countries will be notified in the *Commonwealth of Australia Gazette*.

### **2.5.3 Category 3 applications - Changes to the quality information requiring prior approval**

Category 3 applications involve changes to the quality data of medicines already included on the ARTG, which may or may not render the medicines separate and distinct (and therefore subject to separate registration), and which, in the opinion of the Secretary, do not need to be supported by clinical, non-clinical or bioequivalence data. Refer to the information in Appendices 12 and 13 to determine if the change requires prior approval and submission of a Category 3 application or can be notified to the TGA (see Section 2.5.4). Category 3 applications are provided for under Regulations 16F and 16G.

The types of quality changes subject to a Category 3 application may include, but are not limited to:

- the specifications for the active ingredient, finished product or excipients
- the method of manufacture of the active ingredient
- the manufacturing procedure for the finished product
- the site of manufacture of the active ingredient or the finished product
- the shelf life
- the storage conditions
- the labelling
- the packaging, including container type
- a replacement trade name
- minor changes in formulation.

The type of data to be submitted in support of these applications is discussed in Section 4.4.2.

When submitting a Category 3 application, it may be in the sponsor's interest to provide a justification as to why clinical, non-clinical or bioequivalence data need not be provided.

If, under the provisions of subregulations 16F(2)(a) or 16G(2), the Delegate is of the opinion that an application, submitted as a Category 3 application, needs to be supported by clinical, non-clinical or bioequivalence data, the opinion is regarded administratively as equivalent to a rejection of the application.

Sponsors may request a review of the opinion by the Standing Arbitration Committee (SAC) or alternatively, where the opinion relates to the need for bioequivalence data, by the Pharmaceutical Subcommittee (PSC) of the Australian Drug Evaluation Committee (ADEC) (see Section 3.16.1 for more information about these informal appeal mechanisms).

If no review of such an opinion is requested from one of the above committees (or if a review is unsuccessful), and the sponsor still wishes to pursue the application, two options are available:

- The sponsor may make a new Category 1 or 2 application that includes appropriate clinical, non-clinical or bioequivalence data;

- The sponsor may provide a justification as to why clinical, non-clinical or bioequivalence data need not be provided. The justification and the previous application will be considered for acceptance as a revised Category 3 application. Acceptance will depend upon the data that would now require evaluation. If the revised application is accepted, the clock (see Section 3.5) will be reset to *day one* of the processing period and the evaluation will proceed. If the revised application is not accepted as a Category 3 application, the sponsor may make a new Category 1 or 2 application.

In addition to seeking a review of an opinion about the need for clinical, non-clinical or bioequivalence data by the SAC, sponsors may request that an objection to a Category 3 application based on other matters be reviewed by the SAC.

The formal appeal provisions described in Section 3.16.2 are available in cases where a decision is made to reject a Category 3 application.

#### **2.5.4 Changes to the quality information not requiring prior approval**

After a product has been granted registration in the ARTG, the standard conditions of registration state *inter alia*:

*Changes or variations in respect of any information concerning the registered or listed therapeutic goods, being information that would have been relevant to a decision to register/list the goods on the Register, including information on the formulation of the registered/listed goods or other aspects of their manufacture, and the labelling of the goods, shall forthwith be notified to the Secretary, or the Secretary's delegate appointed for the purposes of Section 28 of the Act, and where necessary, the change or variation shall not be implemented until approved by the Secretary.*

This means that it is a condition of registration that, with limited exceptions, no changes may be made to registered goods without prior approval. The exceptions are safety-related changes to the PI (see Section 4.4.5.1) and changes described as self-assessable, notifiable or not requiring either notification or prior approval in Appendix 12 (*Changes to registered medicines: Changes to the quality information of registered medicines: Notification, Self-assessment and Prior Approval*) and Appendix 13 (*Self-Assessable Changes for Biological Products*).

The self-assessable change provision is intended to allow sponsors to make certain restricted changes, under specific conditions, to the quality aspects of medicines via a self-assessment procedure. The sponsor is responsible for complying with relevant statutory standards and requirements. Although described as self-assessable, a number of general and specific conditions must be complied with. These include:

- the generation of experimental validation data to support the change (see Appendices 12 and 13). These data are not required to be submitted with the notification to the TGA but must be made available to the TGA if requested; and
- a requirement to notify the TGA of the change in most cases (see Appendices 12 and 13).

Self-assessable changes, in general, do not apply to products containing materials of biological origin.

#### **2.5.5 Section 14 exemption**

Medicines supplied in Australia are required, under Section 14(1) of the Act, to comply with the appropriate official standards (typically the British Pharmacopoeia and/or relevant Therapeutic Goods Orders). However, in exceptional circumstances, products may receive an exemption from these requirements.

Exemptions may be applied for as part of an application for registration of a product or requested post-approval (typically as a Category 3 application). Such applications should be accompanied by a justification as to why the exemption is appropriate and will be assessed on a case-by-case basis.

Any data or information that may support the case for an exemption should also be provided. For example, applications for exemption from the letter height requirement of Therapeutic Goods Order 69 (*General requirements for labels for medicines*) should include samples of the proposed labels to demonstrate their legibility.

Exemptions may apply for a particular period of time, to particular batches, or may be permanent. They may also be subject to additional conditions as provided for under Section 15 of the Act.

Approved exemptions are published in *the Commonwealth of Australia Gazette*.

General enquiries regarding applications for Section 14(1) exemptions should be directed to the Head of the Pharmaceutical Chemistry Evaluation Section (PCES) or in the case of biologicals, to the Manager, Prescription Medicines, TGA Laboratories Branch (TGAL).

## 2.6 Special cases of category 1 or 2 applications

See also Sections 4.3.1 (essentially similar medicines), 4.3.2 (orphan drugs) and 4.3.3 (fixed combination products).

### 2.6.1 Orphan drugs

An orphan drug is a medicine, vaccine or *in vivo* diagnostic agent, which is:

- intended to treat, prevent or diagnose a rare disease; or
- must not be commercially viable to supply to treat, prevent or diagnose another disease or condition.

To be eligible for designation as an orphan drug the product must not have been rejected on safety grounds by the TGA, the Food and Drug Administration of the United States of America (FDA), the Medicines and Healthcare Products Regulatory Agency of the United Kingdom (MHRA), the Therapeutic Products Directorate of Canada (TPD), the Medical Products Agency of Sweden (MPA), the Medicines Evaluation Board of the Netherlands (MEB) or the European Medicines Agency (EMA) for use for the disease in question. The product must also have not been registered for use for the disease or condition before 1 January 1998.

The Orphan Drug Program aims to bring orphan drugs to the market by reducing development costs. This is achieved primarily through waiving of the various fees associated with registration. Orphan Drugs can be considered for priority evaluation.

Further information regarding the procedure for designation and registration of orphan drugs is given in Section 4.3.2 and on the TGA website<sup>13</sup>.

### 2.6.2 Priority evaluations

The Director of DSEB may give priority evaluation status to a Category 1 or 2 application. Requests for priority evaluation should be discussed at a pre-submission meeting (Section 3.1.1) and will be considered in circumstances where:

- the active ingredient is a new chemical entity; and

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<sup>13</sup> <http://www.tga.gov.au/docs/html/orphan.htm>

- 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.

Further information regarding priority evaluations is given in Section 3.5.2.

### **2.6.3 Medicines for life-threatening conditions where no satisfactory alternative therapy exists**

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.

### **2.6.4 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 PI 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. Applicants should not routinely submit literature-based data sets where sufficient research-based data are available.

Both the acceptance and the evaluation of literature based submissions will be subject to a flexible, case by case approach, considering the regulatory and clinical history of the medicine. Sponsors should discuss their application with the relevant clinical unit head prior to assembling a submission.

Further information regarding literature based submissions is given in the document *Literature Based Submissions – Points to Consider*<sup>14</sup>.

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<sup>14</sup> <http://www.tga.gov.au/industry/pm-literature-based-submissions.htm>

## 3. The evaluation process – a descriptive overview

The following is a summary of the evaluation process for registration of new medicines. The evaluation and approval processes outlined in Figure 3 are described further in this section.

### 3.1 Prior to submission - considerations

#### 3.1.1 Pre-submission meetings

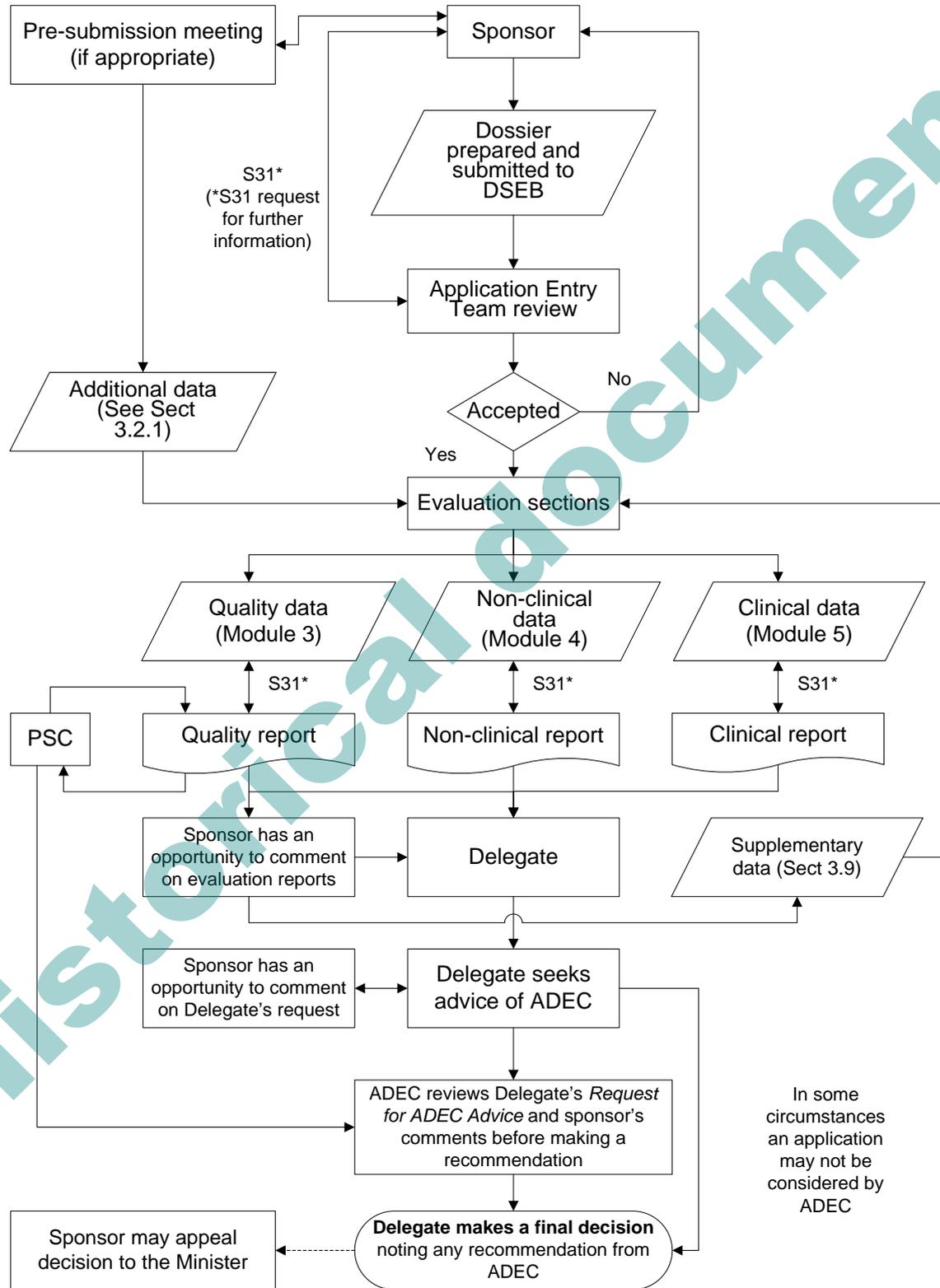
A pre-submission meeting between TGA Delegates and sponsors who intend to submit an application to the DSEB is strongly recommended in certain cases. Such cases include:

- 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. Refer to Sections 2.6.1 and 4.3.2 for details regarding Orphan Drug applications.
- Literature based submissions. Agreement on the search strategy and the databases to be searched is advisable. Refer to Section 2.6.4 and *Literature Based Submissions – Points to Consider*<sup>14</sup> for details regarding literature based submissions.
- Priority evaluations. Refer to Sections 2.6.2 and 3.5.2 for details regarding priority evaluations.
- FDA data package. Refer to Section 2.6.3 for details regarding the use of a FDA data package.
- Additional data. Refer to Section 3.2.1 and Appendix 6 (*Notification and submission of new data*) for details regarding the submission of additional data.
- 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. Refer to Section 4.3.3 for further details regarding issues that need to be addressed.

A pre-submission meeting is also available to sponsors for other applications. Guidelines for meetings with the TGA are provided at Appendix 5 (*Conduct of meetings between TGA and sponsors*).

**Figure 3**

Summary of the evaluation process for category 1 and 2 applications



Historical document

## 3.2 Submission of applications

Applications should be made using the appropriate *DSEB Application Form*<sup>15</sup>. For information regarding the documentation required in the dossier, refer to Sections 4 and 5 and Module 1 (*Module 1: Administrative Information and Prescribing Information For Australia*).

The DSEB requires the submission of all relevant quality data (Module 3), non-clinical data (Module 4) and clinical data (Module 5) to support the application. These modules, together with Module 1 (the Australian specific administrative requirements) and Module 2 (summaries of the entire dossier), comprise the CTD.

Appendix 4 (*DSEB clinical evaluation sections*) gives a complete listing of the therapeutic areas of responsibility for each of the Clinical Evaluation Sections.

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 in accordance with Schedule 9 of the Regulations<sup>16</sup> (see Section 5.2.)

### 3.2.1 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.

- 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.
- 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. (This is described in Section 3.9).

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 (for example, in response to a request under Section 31 of the Act).

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<sup>15</sup> <http://www.tga.gov.au/industry/pm.htm>

<sup>16</sup> <http://www.tga.gov.au/about/fees.htm>

## 3.3 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 unevaluable. If any major deficiencies are found, a Section 31 request for further information will be sent to the sponsor (see Section 3.4.2). The acceptability of any confidentiality statement covering the application will be considered at this time (see Section 4.1.2). 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 (see Fees<sup>16</sup>).

Before the application can be accepted for evaluation, the appropriate evaluation fee must be received by the FSG (see Section 5.2). 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 (according to Regulation 16B) 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.

### 3.3.1 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.

### 3.3.2 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 labelling artwork for their product in preparation for registration.

## 3.4 Evaluation

### 3.4.1 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, for example issuing Section 31 questions, will be through the TGA Delegate. The identity of external evaluators is generally kept confidential.

### 3.4.2 Section 31 requests

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) (see Section 3.16.1).

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.

## 3.5 Processing times

Statutory processing times for applications, which relate to specific evaluation categories, have been established in the Regulations.

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 (see Section 3.4.2), 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.

### 3.5.1 Category 1 and 2 applications

For Category 1 and 2 applications, the processing time comprises a period for acceptance of the application and a period for evaluation, which begins on the day that the TGA notifies acceptance of the application.

Category 1 applications:

- A decision to accept for evaluation or reject an application must be notified to the sponsor within 40 working days from receipt of the application and the evaluation fee;
- If accepted, the application must be evaluated in 255 working days from the date of acceptance.

Category 2 applications:

- A decision to accept for evaluation or reject an application must be notified to the sponsor within 20 working days from receipt of the application and the evaluation fee;
- If accepted the application must be evaluated in 175 working days from the date of acceptance.

For Category 1 and 2 applications, payment of 75% of the evaluation fee is required when the application is submitted. Where the total fee payable is greater than \$100,000, the application may be submitted without payment, and an invoice for 75% of the fee will be sent after screening.

Where the TGA does not complete the processing of a Category 1 or 2 application within the statutory evaluation time, the remaining 25% of the evaluation fee is not payable. However, the evaluation will still proceed to a decision by the Secretary and the sponsor may not market the product until registration is approved.

If an evaluation has not been completed within 255 working days for Category 1 applications or 175 working days for Category 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 as described in Section 3.16.2.

The TGA targets the following mean evaluation times, excluding any clock stops to respond to S31 questions, for different types of application:

- New chemical entities, 150 working days
- New generics, other than additional trade names only, 100 working days

- New indications, 160 working days
- Product Information changes, 90 working days
- Additional trade names only, 45 working days (see Section 4.3.1 for exceptions)
- Other Category 1 applications, 130 working days.

### 3.5.2 Priority evaluations

Formal timeframes have not been established for priority evaluations. It is expected that priority evaluations will be completed as quickly as possible and within the above target timeframes. However, this is dependent upon the receipt of a complete submission and prompt responses to any questions raised.

### 3.5.3 Category 3 applications

For Category 3 applications, there is a single processing period, which begins on the day of lodgement of the application or the day on which the evaluation fee is paid, whichever is the later day. As for Category 1 and Category 2 applications, a Section 31 letter stops the evaluation clock.

Category 3 applications are required:

- to be approved or rejected and the decision notified to the sponsor, or
- to have an objection raised,

within 45 working days of receipt of the application, or payment of the evaluation fee, whichever is the later day.

If, under the provisions of subregulation 16F(3)(b), the Secretary raises an objection to the application, the applicant may respond and provide further information or data.

A further 30 working days from receipt of this response is then allowed for consideration of the response before the application must be approved or rejected.

If the Secretary has not notified the sponsor about the approval or rejection of a Category 3 application within:

- 45 working days of receipt of the application and fees, or
- 30 working days of receipt of the response to an objection, and
- the clock has not been stopped because of a request for further information under Section 31 of the Act,

subregulation 16F(5) provides that the application is deemed to have been approved.

Sponsors should ensure that changes to goods are not made before approval is given, or deemed to have been given, and that allowance is made for events which have *stopped the clock*. Premature implementation of a change would be contrary to the provisions of the Act and penalties may apply. Where the change results in a separate and distinct good (as defined in Section 16 of the Act), formal registration must be effected before supply may occur.

### 3.5.4 Changes not requiring prior approval

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.

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

## 3.6 Overseas rejections and withdrawals during evaluation

Sponsors should notify the TGA of overseas rejections and withdrawals of applications and significant regulatory actions, as specified in Section 4.1.5.

### 3.6.1 Serious adverse reactions reported post submission

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 (see Sections 4.1.4 and 4.1.5).

## 3.7 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 (Section 24D(6) of the Act). 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.

## 3.8 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 for advice, these reports are also provided to ADEC (see Section 3.12).

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 (see also Section 3.11). 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.

## 3.9 Supplementary data

Supplementary data may be submitted after a sponsor has received either or both of the Modules 4 and 5 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 Modules 4 and 5, 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.

For more information on the notification and submission of supplementary data, refer to Appendix 6.

### 3.10 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.

### 3.11 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 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). Please 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<sup>17</sup>). The content and format of the PI are described in Appendix 8 (*Product Information*);

- 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.

### 3.12 Australian Drug Evaluation Committee

The Australian Drug Evaluation Committee (ADEC) is a statutory committee that provides independent advice to the Minister of Health and Ageing or the Secretary of the Department. ADEC's composition and terms of reference enable it to make medical and scientific recommendations relating to applications referred to it by the Minister or the Secretary. The Committee also gives advice to the Minister or Secretary in relation to the import, export, manufacture and distribution of therapeutic goods.

ADEC's core membership consists of eminent medical practitioners, and pharmaceutical scientists or pharmacologists. The particular expertise of associate members is drawn on as appropriate to the applications under consideration.

The associate membership includes a member with experience in the manufacture of therapeutic goods, a toxicologist, general practitioners and medical specialists with expertise that complements that of core members.

ADEC is also supported by the Pharmaceutical Subcommittee (PSC) and the Adverse Drug Reactions Advisory Committee (ADRAC).

The advice ADEC provides includes recommendations about the acceptability in the Australian context of applications for medicine registrations and may advise on the relative priority that should be accorded to the evaluation of individual medicines (see Section 2.6.2 on Priority Evaluations). Applications for registration of medicines evaluated by the DSEB are usually referred to ADEC for advice prior to a decision on registration, for example, consideration of applications for new chemical entities, new routes of administration, new fixed combinations, new therapeutic indications and changes in patient population.

ADEC also reviews proposed rejections by the TGA of applications for new generic products, new formulations, new strengths and major reformulation of existing products. ADEC may review other applications as considered necessary by the Delegate.

ADEC normally meets 6 times a year (2 consecutive days in February, April, June, August, October and December). For ADEC meeting dates refer to the TGA website<sup>18</sup>. The ADEC recommendations, termed ADEC Resolutions, will be sent to the sponsor 5 working days after the ADEC meeting. Ratified minutes of the ADEC meeting at which a Resolution is made will only be available after the following ADEC meeting. The ADEC does not make decisions and its recommendations do not constitute directions to the Secretary or the Secretary's delegate.

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<sup>17</sup> CIOMS Working Group III. *Guidelines for preparing core clinical safety information on drugs*. Geneva, Switzerland: Council for International Organisations of Medical Science; 1995, pages 26-28.

All positive ADEC recommendations are published in the *Commonwealth of Australia Gazette* and are listed on the TGA website. As permitted under Section 61(4) of the Act, the ADEC minutes are also provided to a number of other regulatory agencies overseas.

Further information regarding the role, responsibilities and current membership of ADEC may be obtained from the TGA website<sup>18</sup>.

### 3.12.1 Pharmaceutical Sub-Committee

The Pharmaceutical Sub-Committee (PSC) of ADEC meets every second month, usually on the Monday of the week preceding the ADEC meeting.

The primary role of the PSC is to provide comment to ADEC and the TGA on evaluations of the quality and biopharmaceutical aspects of applications. Applications for a new substance, route of administration or fixed combination would routinely be referred to the PSC during the Evaluation Phase and prior to the *Request for ADEC Advice*. The PSC may consider an application while there are outstanding S31 questions on the quality and biopharmaceutical aspects. The PSC comments on the evaluations and may raise additional issues that can be considered by the TGA during the remainder of the Evaluation Phase.

There are also applications for which the quality and biopharmaceutical evaluations are available at the same time as the non-clinical and clinical evaluations and the application will be presented to the PSC and the ADEC in the same meeting cycle. In these cases, the TGA will ensure that sponsors are given an opportunity either before or after the ADEC meeting to address any issues arising from the PSC meeting.

The PSC recommendations are sent to the sponsor five working days after the PSC meeting. Edited minutes of the PSC meeting are sent to the sponsor after confirmation by the following PSC meeting (that is, approximately two months later). Recommendations of the PSC are not published in the Gazette.

## 3.13 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 (see Section 3.16.2).

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<sup>18</sup> <http://www.tga.gov.au/archive/committees-adece.htm>

## 3.14 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.

## 3.15 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.

The classification criteria for scheduling are set out in the *Guidelines for National Drugs and Poisons Schedule Committee*<sup>19</sup>. A new medicine usually fulfils the classification criteria for a prescription only medicine.

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 (refer to Section 3 of the *Guidelines for National Drugs and Poisons Schedule Committee*).

Further information on scheduling decisions and NDPSC processes is provided in the *Guidelines for National Drugs and Poisons Schedule Committee* available from the NDPSC Secretariat or from the TGA website<sup>19</sup>.

## 3.16 Appeal provisions

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

### 3.16.1 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 under the circumstances as described previously (see Section 2.5.3).

Pharmaceutical Sub-Committee of ADEC and Standing Arbitration Committee:

A SAC *Request for Arbitration* form and additional information may be obtained from:

The Secretary  
Standing Arbitration Committee for Therapeutic Goods  
PO Box 100  
Woden ACT 2606  
Telephone: (02) 6232 8250  
Fax: (02) 6232 8103

<sup>19</sup> <http://www.tga.gov.au/archive/committees-ndpsc.htm>

Requests for review by the PSC should be made in writing to:

Secretary  
Australian Drug Evaluation Committee  
PO Box 100  
Woden ACT 2606

Requests for review by the SAC and the PSC are informal appeal mechanisms, not established under the Act or Regulations and they are not recognised as events which *stop the clock*. However, the clock does stop on the date that TGA raises an objection to a Category 3 application or makes a Section 31 request for further information relating to any category of application. The clock will remain stopped if a request for review is submitted to the SAC or PSC in relation to one of these objections or requests.

The TGA will not regard the lodging of a *request for review* as constituting a formal response that would restart the clock. Accordingly requests for review to the SAC or PSC must include a statement that agrees to the clock being:

- stopped for the period during which the request is under consideration, and
- reset to *day one* (if the review is successful), for requests relating to an opinion that clinical, non-clinical or bioequivalence data are needed for an application submitted as a Category 3 application.

### 3.16.2 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<sup>20</sup>:

The Parliamentary Secretary to the  
Minister for Health and Ageing  
Parliament House  
Canberra ACT 2600

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<sup>20</sup> This name and title of the Minister may change from time to time. The TGA Information Officer will be able to advise the correct information.

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.

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 a 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.

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.

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. Section 24E of the Act covers this situation.

## 3.17 Post-marketing responsibilities

### 3.17.1 Quality

A company or individual who is the registered sponsor of a product is responsible for ensuring that no changes are made to Module 3 (Quality) aspects of the product unless authorised by the TGA.

Subject to stringent conditions, certain changes that carry a low risk to consumers may be made without prior approval and these are listed in Appendices 12 and 13 together with the conditions. When such changes are implemented in accordance with the specific conditions, they are considered authorised by the TGA. Sponsors should not make changes that do not fall within the scope of Appendices 12 and 13, or which do not meet the conditions laid down in Appendices 12 and 13, because this will render the ARTG entry invalid and penalties may apply. See 2.5.4 and Appendices 12 and 13 for more detail on self-assessable changes. Prior written approval must be sought for all other changes.

If the registered sponsor does not personally oversee all steps in manufacture, systems must be in place which allow the sponsor to ensure that no unauthorised change in manufacture is made. The sponsor's responsibility is unaltered when some or all of the data were supplied directly to TGA by a different company or individual, for example, in the following circumstances:

- a company other than the sponsor submits a Drug Master File on an active pharmaceutical ingredient; or
- a product is cross licensed from the manufacturer of a finished product; or
- a company or an individual purchases or otherwise acquires the sponsorship from a former sponsor.

Sponsors are advised to ensure that legal provisions are in place which prohibit changes to any aspect of the product without prior notice to the sponsor. It is the Australian sponsor who is responsible when an unauthorised change is made.

The sponsor is also responsible for ensuring that manufacturing licences are current, including those for overseas sites of manufacture, and that manufacture is conducted to a suitable standard of GMP.

Note that the word *manufacture* is defined in the Act as:

- to produce the goods; or
- to engage in any part of the process of producing the goods or of bringing the goods to their final state, including engaging in the processing, assembling, packaging, labelling, storage, sterilising, testing or releasing for supply of the goods or of any component or ingredient of the goods as part of that process.

### 3.17.2 Pharmacovigilance and other requirements

Registration of a product on the ARTG is subject to a number of conditions that are attached to the TGA approval letter. The *Conditions Standard and Specific Applying to Registered or Listed Therapeutic Goods under Section 28 of the Therapeutic Goods Act 1989* may be found on the TGA website<sup>21</sup>. Any additional special conditions will be notified when the Secretary's decision is advised to the sponsor in the approval letter.

Included in the Standard Conditions of registration is a requirement for the sponsor of the product to inform the TGA of any adverse medicine reactions and safety alerts related to the medicine of which they become aware. The requirements differ for adverse medicine reactions occurring in Australia and those reported in overseas countries. For further details on the requirements for adverse reaction reporting related to prescription medicines regulated by the DSEB see the *Australian Pharmacovigilance Guideline*<sup>22</sup>.

Another condition requires that product recall (or similar regulatory actions) in any overseas country that has relevance to the quality, safety and efficacy of the goods distributed in Australia, be notified to the TGA immediately. Other conditions of registration include conditions related to the sampling and testing of products and manufacturing premises.

### 3.17.3 Periodic safety update reports

Period Safety Update Reports (PSURs) are to be provided annually until the period covered by such reports is not less than three years from the date of the approval letter. The reports are to meet the requirements for PSURs as described in *Note for Guidance on Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs* (CPMP/ICH/228/95)<sup>23</sup>.

Unless separately agreed, the first post-marketing report must be submitted to the TGA no later than 15 calendar months after approval. Subsequent reports must be submitted at least annually from the date of the first submitted report. The annual submission may be made up of two PSURs, each covering six months, or if the sponsor wishes, the six monthly reports may be submitted separately, as they become available. Submission of the report must be within sixty days of the data lock point (the date after which no further data is included in the PSUR) for the report (or, where applicable, the second of the two six monthly reports), as required by CPMP/ICH/228/95. Each

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<sup>21</sup> <http://www.tga.gov.au/pdf/dr4-app04.pdf>

<sup>22</sup> <http://www.tga.gov.au/safety/australian-pharmacovigilance-guideline.htm>

<sup>23</sup> <http://www.tga.gov.au/docs/pdf/euguide/ich/028895en.pdf>

report is to be accompanied by a statement of the amount of each presentation of the product distributed in Australia in the same period (or a period up to the same data lock point).

Historical document

# 4. Data requirements for applications

Information to demonstrate quality, safety and efficacy is to be provided by the sponsor. The sponsor must accept responsibility for the accuracy of the data submitted to the TGA and for all post-approval conditions specified in the TGA approval letter. Significant penalties and/or lapsing of the application may apply to a sponsor who knowingly or recklessly submits false, misleading or inaccurate information with an application to register goods in the ARTG.

## 4.1 General requirements for category 1 applications

Category 1 applications are described in Section 2.5.1. The following requirements generally apply to applications to register a product containing a new active ingredient(s).

### 4.1.1 Presentation of the dossier

The documentation to support a Category 1 application should be provided in the CTD format in accordance with *Volume 2B: Notice to Applicants: Medicinal products for human use. Presentation and format of the dossier CTD*<sup>8, 24</sup> (July 2003)

#### Common technical document (CTD)

Module 1:	<i>Administrative Information and Prescribing Information for Australia</i>
Module 2:	<i>Summaries</i>
Module 3:	<i>Quality</i>
Module 4:	<i>Non-clinical study reports</i>
Module 5:	<i>Clinical study reports</i>

Not all parts will be required for all Category 1 applications. Section 4.3 provides additional detail on the data required for different application types. Section 5 outlines the general administrative details.

### 4.1.2 Confidentiality and freedom of information

Sponsors may request that data contained in their application remain confidential under the provisions of the *Freedom of Information Act 1982* (FOI Act). For FOI requests, the Department of Health and Ageing is not necessarily the final arbiter of whether a document is exempt from disclosure. The Department's practice, consistent with the requirements of the FOI Act, is to consult with the sponsor who submitted the information claimed to be confidential, to:

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<sup>24</sup> Prior to 1 July 2004 the TGA will accept applications to register prescription medicines in both the 'old European Union' (EU) format and the new Common Technical Document (CTD) format. The final date for submissions prepared in the 'old EU' format will be 30 June 2004. After this date, the TGA will only accept applications in the CTD format. For details of the 'old EU' format see: *Volume 2B: Notice to Applicants for Marketing Authorisations for Medicinal Products for Human Use – Presentation and Content of the Dossier* <http://www.tga.gov.au/industry/pm.htm>;

- establish whether release of the information is possible, and
- give the sponsor the opportunity to request a review of any decision made by the TGA to release the sponsor's information under the terms of the FOI Act.

The TGA will not comply with demands for undertakings of confidentiality which seek to limit the lawful use or release of information by the TGA. The TGA has a duty to evaluate therapeutic goods using all information available to it to ensure public safety. Therefore, relevant information may be accessed subject to law<sup>25</sup>.

For further information regarding acceptable confidentiality statements, sponsors should refer to *Module 1: Administrative Information and Prescribing Information For Australia*<sup>7</sup>.

### **4.1.3 Trade name, Product Information and Labels**

#### **4.1.3.1 Acceptability of trade name**

The proposed trade name should not be able to be confused with another product either when spoken or written down. The name should not imply that the product is superior to other products in the same class, or imply a therapeutic use for the product. If the proposed tradename is not acceptable the sponsor will be told why it is not acceptable and be requested to change the name.

The trade name should not be used only to present positive information in the product labelling, nor the generic name is used to present only negative information associated with the product. The trade name should only be used where the information only applies to the characteristics of the branded product, for example, the description, form of presentation, strength, method of use and dosage.

#### **4.1.3.2 Product information**

The draft Product Information (PI) should be submitted in Module 1 of the dossier. For information regarding the format and content of the PI, refer to Appendix 8.

Review of a PI may be required in the following circumstances:

- an application to register a new chemical substance;
- an application to vary the conditions of registration;
- an application to register a new generic product;
- an application to register an additional tradename for a registered product;
- an application to amend the PI not requiring data, for example, editorial changes, safety related notifications.

DSEB may examine a PI for adequacy without receiving a formal application from the sponsor.

For an additional tradename, the PI of the original product must be provided for comparison with the draft PI of the new product. Both documents should be checked by the sponsor before submission to confirm that they are up to date. The original product must be identified in the sponsor's *Letter of Application*.

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<sup>25</sup> Section 25A of the Act states that when evaluating therapeutic goods for registration, protected information about other therapeutic goods may not be used. Protected information relates to an active ingredient first registered less than 5 years previously and refers to information about the active ingredient not in the public domain.

For a new chemical entity, statements in the PI need to be confirmed with data either in the evaluator's report or in the submitted data. It is not permissible to add descriptions of studies that have not been evaluated.

If the review is for an application to amend the conditions of registration, the changes to the PI will generally be limited to the relevant section/s (for example, an application to extend the indications, changes should be proposed for the Clinical Trials, Indications and Dosage and Administration sections). The sponsor should check the proposed PI changes to see that the changes are consistent with the data provided. The sponsor should also check that any new safety information apparent either from the data or from other sources such as a PSUR or PI from another country has been included in the PI, if it is relevant.

#### **4.1.3.3 Boxed warning**

If there is very important safety information concerning a product, it may be included in a boxed warning within the PI. Boxed warnings are applied prospectively, on a case by case basis. The content of the warning must be succinct and draw the attention of the prescriber to information within the main body of the PI. The wording of the boxed warning need not be confined to the text of the approved PI. A boxed warning will be considered for placement on the product packing when justified on an individual basis.

The condition of implementation is that all promotional material must include the boxed warning or include a prominent statement drawing attention to the boxed warning. Brand name reminders must include the notation "See Warning" or "See Boxed Warning", drawing attention to the boxed warning in the PI. For further information, consult the Medicines Australia *Code of Conduct. Edition 14 Guidelines* <sup>26</sup>(Section 3 Promotional Material)

A boxed warning usually has the following format:

- printed in the same or a larger type size than the most common type size used elsewhere in the PI;
- printed in bold;
- laid out so that the text starts with the word WARNING or WARNINGS printed in bold capitals in a type no smaller than the type used in the remainder of the Boxed Warning;
- arranged so that the text will be surrounded by a continuous rectangle printed in bold, with a line thickness agreed to by the Delegate;
- positioned in the PI as to be readily and immediately apparent to the reader.

Boxed warnings, either as an addition, change or amendment to the PI, are usually considered by ADEC.

#### **4.1.3.4 Marketed and unmarketed product presentations**

A sponsor must have a PI for all registered medicines, however, not all registered presentations may be marketed. A sponsor may choose to have and maintain two PI documents, one for all registered product presentations or non-marketed product presentations and another for marketed product presentations. Each document requires review and the documents must be consistent regarding all information except presentation and information specific for the omitted presentations.

#### **4.1.3.5 Consumer medicine information**

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<sup>26</sup> <http://www.medicinesaustralia.com.au>

A draft Consumer Medicine Information (CMI, also known as Patient Information) should be submitted in Module 1 with all applications that will result in a new ARTG entry. This requirement includes applications that result in a new *grouped* entry (for example new indications, change of product name). The CMI should be consistent with the PI and cannot be promotional. For information regarding the content and format of the CMI, refer to Schedule 12 of the Regulations<sup>3</sup>.

#### **4.1.3.6 Package inserts**

The Act requires that the presentation of the goods be acceptable. This includes the labelling and the content of any package insert that will be supplied with the product. In general, a package insert does not require evaluation by the TGA. However, the TGA may review package inserts if they contain information relating to the safe and appropriate use of the goods. An example may be where obligatory labelling information does not fit on the label, and so is included in a package insert instead.

It is the sponsor's responsibility to ensure that all package inserts remain consistent with the label, PI and/or CMI, as appropriate. It is also important that package inserts be non-promotional.

The PI should be supplied as a package insert for products for parenteral use. However, for self-administered injections, the Consumer Medicine Information may be included with the PI as the package insert.

Package inserts must be provided to the TGA. They must be included as part of the Module 1 data for evaluation if they include obligatory labelling information.

#### **4.1.3.7 Labels**

The Australian standard for labels for medicines, TGO 69 *General Requirements for Labels for Medicines*<sup>27</sup>, should be complied with unless otherwise exempted (see Section 2.5.5). Sponsors should note that labels should also meet the requirements of other Commonwealth, State and Territory legislation.

Copies of artworks for labels, including actual size copies and an indication of the intended colours which are proposed for use in Australia should be included in Module 1 of the application.

Label colours should take into account the fact that dispensers and patients may have varying degrees of colour blindness.

#### **4.1.4 Individual patient data**

Individual patient data (IPD) from each clinical trial are not required to be included in the documentation at the time of application, except in the case of any bioavailability studies where individual patient data for plasma or serum concentrations and derived pharmacokinetic data are required. However, IPD may be requested and should be available.

Individual patient data may be included in the documentation if the sponsor considers it appropriate. Note: Individual Case Report Forms are not accepted as individual patient data.

Before an application is submitted, sponsors should ensure that IPD are readily available in a format suitable for submission in either the EU or USA. Generally this is tabulated patient data that includes clinical and laboratory monitoring results formatted to show a relationship to individual patients. A statement that these data can be provided must be supplied and inserted into Module 1 of the dossier. Any studies for which IPD are unavailable should be identified in the statement.

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<sup>27</sup> <http://www.comlaw.gov.au/Details/F2009C00264>

Individual patient data, if not supplied, may be requested during the evaluation period and, if a request for these data is not met within 15 working days, the application will usually lapse. Individual patient data may be requested by the TGA:

- to support a particular study if, during the evaluation, there is any reason to doubt the analysis or conclusions reached;
- if, after registration, the application is selected for auditing of the summary results and conclusions. Selection for auditing will be on a random basis, unless an overseas rejection is being investigated.

If a marketing application for the medicine has been rejected in the USA or Canada before or during the Australian evaluation process, for reasons related to the clinical data in any way, full IPD must always be available and may be required to be submitted in Australia.

Sponsors must declare whether a marketing application for the medicine has been rejected in the USA or Canada prior to lodgement of the application in Australia. This statement should be included in Module 1 of the dossier. If the medicine has been rejected, repeatedly deferred or withdrawn in Canada or withdrawn or denied approval in the USA, then full IPD may be required. If rejection in the USA or Canada occurs during the Australian evaluation process, the TGA should be informed.

#### **4.1.5 Overseas status**

The overseas regulatory status of applications for the product<sup>7</sup> should be included in Module 1 of the CTD dossier.

An updated overseas status report is required at the time of ADEC consideration (see Section 3.11) or the time at which the TGA Delegate decides on approval if not referred to ADEC. This should detail approvals (with indications) and deferrals, withdrawals and rejections with reasons in each case. For European submissions, sponsors should indicate if applications are via the centralised or mutual recognition procedure. For applications by the centralised procedure, the primary and secondary rapporteurs should be identified; for applications by the mutual recognition procedure, the reference Member State should be identified.

#### **4.1.6 International evaluation reports**

Even where a Category 2 classification (see Section 2.5.2) is not being sought for an application, the sponsor is encouraged to provide copies of evaluations from other regulatory agencies or authorisation for the TGA to obtain evaluations from other regulatory agencies, as this may expedite the evaluation process.

Where there is an intention to use an overseas evaluation report in the evaluation, the TGA will request the sponsor to provide a declaration which includes full details of any differences between the data submitted in Australia and the data submitted in the other countries. Where significant differences exist, these should be identified and commented upon in general terms. Significant differences may reduce the ability of the TGA to use overseas reports to expedite evaluation processes. If any significant, undisclosed differences are found subsequently by the TGA, the application may be rejected.

#### **4.1.7 Drug Master Files and Certificates of Suitability**

An application to register a new medicine or vary the registration of an existing medicine may make reference to a Drug Master File (DMF). A DMF may concern any aspect of a medicine that is:

- submitted by a manufacturer other than a finished product sponsor. For example, the manufacturer of a drug substance (active pharmaceutical ingredient), the manufacturer of a starting material or intermediate used to produce a drug substance by a different manufacturer; or
- a common feature of more than one product (for example, sterility test procedures); or

- some other matter which is conveniently dealt with by means of a master file procedure (for example, the analytical procedure used in a biopharmaceutical study).

The companies that submit DMF receive a unique file number in the acknowledgement letter from TGA. This file number should be quoted by the product sponsor whenever reference is made to the DMF. It is the responsibility of the company that submitted the DMF to advise product sponsors of the TGA file number.

For a medicinal substance that is the subject of a monograph in the European Pharmacopoeia (Ph. Eur.), the sponsor may submit a European Directorate for the Quality of Medicines (EDQM) issued Certificate of Suitability of Monographs of the European Pharmacopoeia (CEP) in lieu of a DMF. Subject to the scope and procedures of the certification process, the TGA also accepts a CEP in lieu of a DMF for a drug substance (including amino acids, antibiotics and other organic active substances whose manufacture may include a fermentation or bioconversion step) in registration and variation applications.

Procedures relating to DMFs and CEPs are outlined in more detail in Appendix 11 (*Drug Master Files and Certificates of Suitability*).

GMP clearance by the TGA is required for sites of manufacture of drug substances that are the subject of DMFs or CEPs, and it is the responsibility of the sponsor to obtain such clearances. This documentation should be included in Module 1 of the CTD.

#### **4.1.8 Summary of biopharmaceutical studies**

Australia's requirements for biopharmaceutical studies are aligned with the Committee for Medicinal Products for Human Use (CHMP) *Note for Guidance on the Investigation of Bioavailability and Bioequivalence* (CPMP/EWP/QWP/1401/98<sup>28</sup>) which is formally adopted in Australia. In relation to the content of biopharmaceutical study reports, this guideline states that:

*The report of a bioavailability or bioequivalence study should give the complete documentation of its protocol, conduct and evaluation complying with GCP-rules and related EU and ICH E3 guidelines. This implies that the authenticity of the whole report is attested by the signature of the principal investigator. The responsible investigator(s) should sign for their respective sections of the report.*

The biopharmaceutical study report must be signed by the principal investigator, either in an unqualified manner or clearly taking responsibility for all aspects of the study conduct for which they may reasonably be held responsible.

In addition to the requirements outlined in the CHMP *Note for Guidance on Investigation of Bioavailability and Bioequivalence*, the DSEB also encourages applicants to complete the optional *summary form*. The summary form is designed to assist the DSEB in examining the relevance and adequacy of biopharmaceutical data prior to acceptance of an application. Further information regarding completion of the *summary form* is provided in Appendix 15.

Completed Summary Forms may be included as part of Module 1 in applications submitted in CTD format.

If an applicant wishes to justify not providing a biopharmaceutical study, Appendix 15 (*Biopharmaceutical studies*) provides a minimum set of issues to be addressed in any justification.

#### **4.1.9 Good manufacturing practice (GMP)**

For all medicines, irrespective of country of origin, it is expected that key manufacturing and/or processing steps in the production of bulk active drugs and finished pharmaceutical products are performed in plants with acceptable GMP standards.

<sup>28</sup> <http://www.tga.gov.au/pdf/euguide/ewp140198entga.pdf>

Manufacturing sites within Australia should comply with Australian GMP requirements and be licensed. These requirements are set out in Part IV of the Act and described in the TGA document *Australian Code of Good Manufacturing Practice for Medicinal Products*<sup>29</sup>. An updated list of manufacturing principles established under the Act is provided on the TGA website<sup>29</sup>.

The Act also requires the standard of manufacture and quality control of therapeutic goods manufactured overseas be considered before inclusion of therapeutic goods in the ARTG. Therefore a sponsor applying to the TGA to register or list a therapeutic good manufactured outside Australia must provide an acceptable form of evidence to show that the manufacture of the goods is of an acceptable standard.

Certification requirements for overseas manufacturers are set out in the TGA document, *Standard of Overseas Manufacturers*<sup>29</sup>. This guideline is intended to provide information on what is regarded by the TGA as an acceptable form of evidence, and guide sponsors and manufacturers in the submission of that evidence to the TGA for assessment. The document is not intended to provide a definitive list of forms of evidence that are considered acceptable or unacceptable.

Evidence of the standard of manufacture submitted will be reviewed by the Manufacturers Assessment Section of TGA (MAS) and information on the standard of each manufacturing site operated by overseas manufacturers will be kept on a computer database maintained by MAS.

#### **4.1.9.1 GMP clearance**

Applications for the registration of a prescription medicine in the ARTG may be delayed or rejected due to a lack of acceptable evidence of the standard of manufacture of the medicine. The TGA will not usually delay acceptance of Category 1 applications if the only question raised is the availability of evidence of the standard of manufacture. However, acceptable evidence must be provided to the TGA before the application can be approved. To avoid delays or possible rejection, sponsors are requested to obtain GMP clearance prior to submitting their application.

A GMP clearance letter is required to be submitted with a Category 3 application or a Self-Assessable Notification that includes a change in overseas manufacturing sites (see *Guidelines on Standard of Overseas Manufacturers*<sup>29</sup>).

To request a clearance of GMP evidence sponsors must complete an *Overseas Manufacturer GMP Clearance Application Form*<sup>30</sup> for each manufacturing site, attach the relevant evidence of the manufacturing standard and forward it to the MAS, as instructed on the form. The GMP Clearance Application Form is available on the TGA website<sup>29</sup>.

A sponsor may submit a request for clearance at any time prior to the submission of an application to the DSEB. MAS will assess the application and evidence submitted in accordance with the current edition of the *Standard of Overseas Manufacturers*. A response detailing the result of the assessment will be returned to the sponsor. The response to the sponsor will confirm the manufacturing site address, what product type or processes the evidence covers, the steps in manufacture, whether the evidence is acceptable and a date prior to which new evidence must be submitted. A copy of this response can be included with an application to the TGA for listing or registration of therapeutic goods and may be used by the sponsor to whom it is issued for other applications where the scope of manufacture is the same.

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<sup>29</sup> <http://www.tga.gov.au/industry/manuf.htm>

<sup>30</sup> <http://www.tga.gov.au/manuf/gmpclform.htm>

GMP clearance letters, when available, should be included in Module 1.5 of the dossier. For further details of the information to be provided, sponsors should consult *Module 1: Administrative Information and Prescribing Information For Australia*<sup>7</sup>.

#### **4.1.10 Provisional ARTG record**

Sponsors should include a Provisional ARTG Record (PAR) with each Category 1 application and with any other application which proposes to change ARTG details. The information included on the provisional entry is included on the Premier tracking system and is updated as required during evaluation of the application. At the conclusion of the evaluation, the final information becomes the Register entry for the product. A template for a PAR is available on the TGA website.

#### **4.1.11 General requirements for the competence of calibration and testing laboratories**

Laboratory data on chemical, quality and biological matters should be generated at a standard consistent with an acceptable code of Good Control Laboratory Practice. This would include ISO/IEC/EN 17025 (formerly ISO Guide 25 & EN45001) *General Requirements for the Competence of Calibration and Testing Laboratories*<sup>31</sup>.

#### **4.1.12 Good laboratory practice**

Non-clinical safety studies (including toxicokinetic studies) should be conducted in accordance with an appropriate code of Good Laboratory Practice (GLP). In most countries this is the *OECD Principles of Good Laboratory Practice*<sup>32</sup>. In some countries a national variant of the OECD Principles of GLP applies, for example, the US FDA CFR Part 58 - *Good Laboratory Practice for Nonclinical Laboratory Studies*<sup>33</sup>.

Australian studies should be conducted in accordance with the OECD Principles of GLP and the facilities undertaking such studies should be in the Australian GLP compliance-monitoring program. Study data that is generated overseas should also be generated in accordance with the OECD Principles of GLP or the country's national variant. These facilities should also be in their national GLP compliance-monitoring program or be able to demonstrate GLP compliance by an equivalent means, for example, in the US by means of routine GLP inspection by the US FDA.

The study director should sign each report and quality assurance statements should be provided for each study. An explanation must be given when safety studies are not conducted in accordance with the relevant code of GLP or where such documentation is not available.

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<sup>31</sup> <http://www.fasor.com/iso25/>.

<sup>32</sup> [http://www.oecd.org/document/63/0,2340,en\\_2649\\_34381\\_2346175\\_1\\_1\\_1\\_1.00.html](http://www.oecd.org/document/63/0,2340,en_2649_34381_2346175_1_1_1_1.00.html)

<sup>33</sup> [http://www.fda.gov/ora/compliance\\_ref/bimo/7348\\_808/default.htm](http://www.fda.gov/ora/compliance_ref/bimo/7348_808/default.htm)

#### 4.1.13 Good clinical practice

TGA requires that all phases of clinical investigation be conducted in accordance with acceptable guidelines for Good Clinical Practice (GCP), such as the CHMP *Note for Guidance on Good Clinical Research Practice* (CPMP/ICH/135/95)<sup>34</sup>. The Clinical Overview (Module 2.5) should assess the quality of the design and performance of the studies, and include a statement regarding GCP compliance. Comment should be provided on any studies not complying with GCP and the reasons why the guidelines were not applied.

#### 4.1.14 Ethical certification

The *Note for Guidance on Good Clinical Practice* (CPMP/ICH/135/95)<sup>35</sup> states "Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s)." For trials conducted in Australia applicable regulatory requirements include the National Health and Medical Research Council (NHMRC) *National Statement on Ethical Conduct in Research Involving Humans*.<sup>36</sup> The sponsor must be able to provide the TGA with any relevant documentation, including approval letters from Human Research Ethics Committees (HRECs), specimen subject consent forms and patient information sheets, within three months of any request.

Any studies not conducted in accordance with the above should be identified and the reasons given (Clinical Overview in Module 2 of CTD).

#### 4.1.15 Certified Product Details (CPD)

The TGA will normally request a summary of certain details about the product, its formulation and quality control to assist the TGA Laboratories should testing of the product be required. For more details, see Appendix 7 (*Certified product details*).

A form for this purpose is available on the TGA website<sup>37</sup>.

## 4.2 General requirements for category 2 applications

Category 2 applications are described in Section 2.5.2. The general requirements that apply to Category 1 applications (Section 4.1) are also applicable to Category 2 applications. There are also a number of unique requirements relating to Category 2 applications.

The TGA will not initiate or identify a Category 2 application. The onus is on the sponsor to identify the application as Category 2 and to provide two independent overseas evaluation reports or liaise with the TGA to have them provided. For a list of acceptable countries, see Section 2.5.2.

A Category 2 application will only be regarded as submitted when all of the statutory requirements have been satisfied, including the receipt by TGA of the following:

- relevant overseas evaluation reports;
- data supporting the application;

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<sup>34</sup> <http://www.tga.gov.au/industry/clinical-trials-note-ich13595.htm>

<sup>35</sup> <http://www.tga.gov.au/pdf/euguide/ich13595.pdf>

<sup>36</sup> <http://www.nhmrc.gov.au/issues/researchethics.htm>

<sup>37</sup> <http://www.tga.gov.au>

- a declaration that includes full details of any differences between the data submitted in Australia and the data submitted in the two *acceptable countries* from which evaluation reports have been provided. This includes data submitted in response to agency questions.

If any significant, undisclosed differences are found by the TGA, the application will revert to a Category 1 application.

## 4.3 Requirements for special cases of category 1 and 2 applications

### 4.3.1 Essentially similar medicines

#### Definitions

The EC guidelines<sup>38</sup> state that a product *is essentially similar* to another product if:

- it has the same qualitative and quantitative composition in terms of active principles/substances; and
- the same pharmaceutical form; and
- is bioequivalent

unless it is apparent in the light of scientific knowledge that it differs significantly from the original product as regards safety or efficacy.

By extension, the concept of 'essentially similar' also applies to different immediate release oral dosage forms (for example, tablets and capsules) which contain the same active ingredients.

Medicines that are *essentially similar* to an *innovator product* may be designated *generics*.

#### Types of applications

Applications for *essentially similar* medicines can be made in Australia under a number of different circumstances:

- *In lieu* of safety and efficacy data, an appropriate bioavailability study (or studies) should normally be submitted. Provided that the essentially similar product has a sufficiently similar plasma concentration/time profile to a leading brand in Australia, the two products may be considered bioequivalent. Appendix 15 provides *inter alia* guidance on types of applications for which bioavailability data need not be submitted. In other cases, the applicant must justify not providing bioavailability data. A minimum list of points to be addressed in such a justification may be found in Appendix 15. The comparative impurity profile of the two products will also be relevant to whether or not safety data are required on the essentially similar brand.

If the PI and/or CMI are different in content to those of the already registered brand, safety and/or efficacy data may be needed.

If bioequivalence has been demonstrated with a product not available in Australia, the identity of that product with a leading brand available in Australia must be demonstrated. Comparative dissolution data alone would not normally be adequate bridging data in this situation.

Appendix 15 (*Biopharmaceutic studies*) provides further details on biopharmaceutic study

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<sup>38</sup> The Rules Governing Medicinal Products in the European Community”, Volume 2A, page 12.

requirements. Suprabioavailable products will be assessed on a case by case basis.

Applications to register essentially similar products are classified as Category 1 applications, and therefore a statutory time limit of 255 working days will apply.

- A sponsor may register an additional brand of its own already registered brand, in which case the application should consist of:
  - **either** an assurance that all Module 3 aspects of the new brand are identical to the already registered brand except for labelling, **or** information on any differences together with an assurance that all other Module 3 aspects are identical;
  - a provisional ARTG record, which should be based on the ARTG entry for the registered brand;
  - labelling for the new brand;
  - a PI document for the new brand;
  - a CMI for the new brand;
  - **either** a statement that the PI and CMI are identical to those of the existing brand, **or** a list of the differences.

If the PI and/or CMI are not identical to those of the already registered brand, safety and/or efficacy data may be needed depending on the case.

- In the case of cross licensing a sponsor authorises TGA to use information on its already registered brand for the benefit of another sponsor. In this case, the new brand will be identical to the first brand or at least very similar. The application would normally comprise:
  - all components of (ii) above;
  - a letter from the sponsor of the already registered brand allowing TGA to use information in the registration file on behalf of the applicant and stating whether or not the applicant may view the information on file.

If the PI and/or CMI are not identical to those of the already registered brand, safety and/or efficacy data may be needed depending on the case.

In law an application to register an additional trade name for an already registered product by the same sponsor is subject to the same timeframe as a Category 1 application. However, where possible, the TGA will complete the review in a non-statutory target timeframe of 45 working days. The reduced review time is more likely to be achieved if the PI for the originator product has recently been reviewed and approved. If the originator PI is not current and up to date, or if there are Module 3 changes other than labelling, review times may extend beyond 45 working days.

Only abbreviated Module 1 data are required for such applications.

### **4.3.2 Orphan drugs**

Orphan drug products are medicines used in the treatment, prevention or diagnosis of rare diseases. For further information on the criteria for eligibility as an orphan drug see Section 2.6.1. Orphan drugs may also meet the criteria for priority review (see Section 2.6.2).

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.

#### **4.3.2.1 Application for designation of orphan drug status**

A sponsor planning to submit an application for orphan drug designation should first contact the relevant Clinical Evaluation stream of the DSEB to discuss preparation of an application for designation.

After submission of the application for designation the TGA will advise the applicant of its decision. If orphan status is granted, the designation will be published in the *Commonwealth of Australia Gazette* and the ADEC advised.

#### **4.3.2.2 Application for orphan drug registration**

The quality, efficacy and safety of orphan drugs will be assessed at the same standard as for other registered medicines.

In situations where the FDA has approved an orphan drug for marketing in the USA, the TGA will usually accept the same data as those submitted to the FDA, with the following additions:

- a set of current specifications for the finished product as it is to be supplied in Australia;
- evidence of GMP clearance by TGA for any overseas sites of manufacture of the active pharmaceutical ingredient and finished product (including packaging and sterilisation);
- a provisional ARTG record;
- draft Australian labels;
- draft Australian PI;
- draft CMI.

Evaluation may be expedited if the applicant is prepared to assist the TGA in obtaining copies of the US evaluation report. This situation will not apply if FDA approval is not recent (more than 2 years) and/or the sponsor has become aware of any additional safety issues.

Where the FDA has rejected an orphan drug for marketing in the USA on grounds other than clinical safety, the TGA will accept the application if additional data that address the objections raised by the FDA are included.

TGA will waive 100% of the evaluation fee for orphan drugs to be included in the ARTG. Annual charges are payable and the sponsor may be able to apply for a reduction on the basis of low volume and low value.

The TGA requirement for post marketing reports (see Section 3.17) is determined on a case by case basis. This will usually be in the form of an international PSUR, though, at times, other information may be requested.

#### **4.3.2.3 Application to vary conditions of orphan drug registration**

When an orphan drug has been registered, and the sponsor wishes an extension of indications for another patient population satisfying orphan criteria, the TGA will treat the applications for designation and registration on their merits.

The sponsor should identify any parts of the data submitted with the first application that have been expanded or otherwise changed in the new application.

Any proposed changes to Module 3 aspects of already registered orphan drug products are treated in the same way as any other registered medicine.

#### **4.3.3 Fixed combination products**

Sponsors wishing to register a new fixed combination product should justify the particular combination and the type and extent of data to be submitted. The justification should be discussed at a pre-submission meeting (Section 3.1.1), focusing on the issues outlined in part 1 the guidance

on *Fixed Combination Medicinal Products*<sup>39</sup> (CPMP/EWP/240/95), or separately raised with the Delegate before submission.

The sponsor's justification will be reviewed by TGA and the sponsor will be advised whether the fixed dose combination will be acceptable for review. If the TGA proposes that the application is not acceptable for evaluation, the advice of ADEC will be sought.

If the fixed-combination product contains active ingredients not currently included in combination on the ARTG, then non-clinical and clinical studies of the combination should be submitted. Otherwise a justification for their exclusion will need to be provided by the sponsor.

#### **4.3.4 Products containing or consisting of genetically modified organisms**

Genetically modified organism (GMO) means an organism in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination.

Regulatory guidelines for products containing or consisting of GMOs are discussed in Appendix 21 (*Medicines produced by genetic manipulation*).

#### **4.3.5 Products containing ingredients of human or animal origin**

Any materials of human or animal origin used as active ingredients, excipients or during manufacture (for example, fermentation medium) need to be assessed for viral and prion safety.

The TGA has a step-wise risk management approach to the assessment of ruminant materials used in therapeutic goods. This approach has been endorsed by the NHMRC Special Expert Committee on Transmissible Spongiform Encephalopathies (SECTSE). If a therapeutic good is injectable, implantable, or introduced through the intra-ocular or intra-tracheal routes and it either contains or is manufactured using materials or reagents of ruminant origin, it must be evaluated by the TGA for TSE safety. For further information see Appendix 10 (*Ingredients of human and animal origin*) and the TGA website<sup>40</sup>.

#### **4.3.6 Products and use of human embryos, human embryonic stem cells and materials derived therefrom**

For products that are manufactured using a human embryo or human embryonic stem cell, or any material sourced from a human embryo or human embryonic stem cell, there must be a statement of origin in the PI and the Consumer Medicine Information. (See Appendix 24: *Information about therapeutic goods manufactured using human embryos, human embryonic stem cells and materials derived therefrom*).

In addition, where information is provided to the TGA (as part of an application for registration of a prescription medicine) that refers to the use of human embryos, human embryonic stem cells (or materials sourced from human embryos or human embryonic stem cells) in research undertaken in the development of the medicine, then the draft PI and CMI provided to the TGA should provide a statement to this effect. Subject to approval of the PI by the TGA, and following registration of the medicine, the CMI is also expected to include a similar statement in line with the PI.

A declaration concerning the use of such material must be completed as part of Module 1.

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<sup>39</sup> <http://www.tga.gov.au/docs/pdf/euguide/vol3c/3cc10aen.pdf>

<sup>40</sup> <http://www.tga.gov.au/industry/tse-policy.htm>

#### **4.3.7 Products containing antibiotics**

In response to the Joint Expert Technical Advisory Committee on Antibiotic Resistance (JETACAR) Report (released in October 1999) and The Commonwealth Government Response to the Report of the Joint Expert Technical Advisory Committee on Antibiotic Resistance, the TGA anticipates that antibiotic resistance data will need to be submitted in Australia in the future. When finalised, relevant guidelines will be posted on the TGA website.

Historical document

#### 4.3.8 Products for use in special populations

The Clinical Summary (Module 2.7 of the CTD) emphasises the need for a consideration of the use of medicines in special populations. These considerations include:

- individualisation of dosage and the need for modifications of dosage for specific subgroups (for example, paediatric or geriatric subjects, subjects with hepatic or renal impairment), and data relevant to dose-response or concentration response (PK/PD) relationships;
- analyses across multiple studies to evaluate effects of major demographic factors (age, sex, and race) and of other predefined or relevant intrinsic and extrinsic factors (for example, disease severity, prior treatment, concomitant illness, concomitant drugs, alcohol, tobacco, and body weight) on efficacy;
- routine analysis of efficacy in the paediatric population in applications for a proposed indication that occurs in children.

Sponsors are encouraged to consider whether their products are likely to be used in children, and if so, to discuss with the TGA how to make available paediatric formulations and to update the PI document with information on paediatric use. Guidelines dealing with paediatric data generation and facilitating the extrapolation of data from one patient population to another include:

- *Note for Guidance on Clinical Investigation of Medicinal Products in the Paediatric Population;*
- *Note for Guidance on Ethnic Factors in the Acceptability of Foreign Clinical Data*<sup>39</sup>.

The TGA would strongly encourage sponsors with paediatric data and products to apply for registration. Currently, the TGA has a number of mechanisms in place to encourage the submission of paediatric data packages, including:

- the Orphan Drug Program, which waives all registration fees conditions with a prevalence of intended users of less than 2000 per year (see Section 2.6.1);
- modified literature-based submissions to facilitate submission of modified packages based on existing published data (see Section 2.6.4).

## 4.4 Requirements for modified applications

### 4.4.1 Category 1 applications for other than new active pharmaceutical ingredients or new combinations

Any application that does not involve the registration of a medicine containing a new active ingredient, but still contains either clinical, non-clinical or bioavailability data is also classified as a Category 1 application. Such applications may include:

- a different formulation
- a different strength or size (disregarding pack size)
- a different dosage form or mode of administration
- a generic product
- different indications
- different directions for use, including different patient populations
- certain non-safety related changes to PI

The amount and type of data for Category 1 applications (to make changes to a registered product) will vary depending on the nature of the product and the proposed use. Summaries and overviews should refer to the data submitted and should confirm the status of previously submitted data.

For some Category 1 applications to amend the PI, a Module 2 may not be required. The requirement for inclusion of a summary or clinical overview in these applications depends on the type of amendment that is being made to the PI. For example, insertion of new dosage information will usually require a summary and overview; a minor update to the Clinical Pharmacology section of the PI may not require a summary and overview. Applications should be discussed with the TGA if the sponsor is not sure whether summaries and overviews are required.

For a medicine that does not fall within the definition of *essential similarity*, and therefore does not benefit from the exemption from providing the results from non-clinical studies and clinical trials, the results of appropriate non-clinical studies and/or appropriate clinical trials should be provided.

### 4.4.2 Category 3 applications for quality changes requiring prior approval

The documentation to support a Category 3 application should be provided in the CTD format in accordance with *Volume 2B: Notice to Applicants: Medicinal products for human use. Presentation and format of the dossier CTD*<sup>8</sup> (July 2003)

Changes to the quality aspects of a registered good cannot be made unless the sponsor seeks prior approval via a Category 3 application, with supporting data, or the proposed change is identified as notifiable, self-assessable or not requiring either self-assessment or notification (see Appendices 12 and 13).

To facilitate a Category 3 application, a sponsor must submit:

- a letter of application setting out the reasons for the application
- an application form<sup>3</sup>;
- details of the proposed quality change, with appropriate supportive data (see details of data requirements in Part C of Appendix 12);
- the sponsor section of any relevant DMF or PMF;

- an assurance that:
- No aspects of the quality data have been changed, including manufacturing procedures and equipment and raw material and finished product specifications, other than changes proposed in this application and those made in conformity with the guideline: *Changes to the quality information of registered medicines: Notification, Self-assessment and Prior Approval*.
- the evaluation fee<sup>16</sup>.

Upon completion of the evaluation, TGA may also request an updated copy of the CPD (see Section 4.1.15).

Section 3.5.3 describes the statutory timeframes for evaluation of Category 3 applications. Sponsors should note that, under the conditions outlined in this section, Category 3 applications may be deemed to have been approved without formal notification by the TGA if the statutory time frame has elapsed.

#### **4.4.3 Other quality changes**

As outlined in Section 2.5.4, there are some changes or variations to information concerning goods registered on the ARTG that do not require prior approval. These include safety-related changes to PI (see Section 4.4.5.1) and certain quality aspects of the medicine.

Appendices 12 and 13 identify whether a proposed change requires prior approval, or whether a change can be made without prior approval.

Self-assessable changes are detailed in Part B of Appendix 12 and Appendix 13 and are subject to the conditions outlined in these appendices. If the specified conditions are not met, prior approval is required.

Notifications or self-assessable changes are not required to be supported by documentation in the CTD format. However, if applicable, the sponsor must generate experimental validation data to support the change. The TGA reserves the right to request copies of the experimental validation data at its discretion or follow up the validation during a GMP audit.

Sponsors should note that implementation of a change that requires prior approval, when such approval has not been obtained, would be contrary to the provisions of the Act and penalties may apply.

#### **4.4.4 Additional packs (Sample packs)**

All packs proposed for supply for human use, including *sample, starter or professional* packs, should be listed in any registration application and are subject to the usual requirements for quality control, stability testing and labelling. A pack which contains more than one product, for example, two strengths of a tablet, or which explicitly or implicitly suggests a dosage regimen, would be scrutinised for consistency with dosage recommendations in the PI.

A new sample pack which is intended for human use does not require a new registration or listing unless it is a separate and distinct good from the existing registered or listed product, as described in Section 16 of the Act. A different container size from the registered or listed product does not constitute a separate and distinct good, but a different container type does. The addition of a new sample pack that is not a separate and distinct good only requires an application to vary an ARTG entry.

#### **4.4.5 Product information**

A draft PI should be submitted (Module 1) with all Category 1 and 2 applications and Category 3 applications that will result in a new ARTG entry, for example, reformulations and new container types. For information regarding the format and content of the PI, refer to Appendix 8.

A Category 3 application may result in consequential changes to the PI. If the subject of such a Category 3 application is to be implemented immediately after approval, a copy of the draft PI should be included in the application. Alternatively, if the subject of the Category 3 application is not to be implemented immediately, such changes to the PI may be notified to the TGA following approval of the Category 3 application (see Section 4.4.5.2).

Category 3 applications seeking changes to the quality aspects cited in the PI should include a copy of the draft PI in the application.

#### **4.4.5.1 Safety-related changes to the product information**

Safety-related changes to the PI may be made by the Sponsor without prior approval. By definition [Section 9D(2) of the Act] safety related changes must only reduce the patient population or add a warning, precaution, contraindication or adverse event to the approved PI document. Indications may be removed from the PI as a safety-related change.

To facilitate a safety related notification, the sponsor must submit to TGA:

- a letter outlining the reasons for the notification;
- a copy of the approved PI on which the changes have been clearly identified;
- an assurance that no other changes have been made to the PI document and that the changes are supported by data in the sponsor's possession;
- a processing fee<sup>16</sup>.

The TGA must be notified of safety-related changes within 5 working days of their implementation. TGA will acknowledge receipt of the safety-related notification, however, this does not imply that the text has been reviewed or approved. Any subsequent printed version of the PI must show the date of the last TGA approval, if applicable, and the date of the most recent safety related notification. If these changes are significant, the sponsor should consider communicating them to the prescribers and pharmacists, and if necessary, to consumers via the CMI.

#### **4.4.5.2 Changes to the quality aspects of the PI**

Changes to the quality aspects of the PI that may be made by the Sponsor without prior approval are described in Appendix 12. To facilitate such a self-assessable notification, the sponsor must submit to TGA:

- a letter outlining the reasons for the notification;
- a copy of the approved PI on which the changes have been clearly identified and a clean copy of the amended PI;
- an assurance that no other changes have been made to the PI document and that the changes are supported by data in the sponsor's possession;
- a processing fee<sup>16</sup>.

#### **4.4.5.3 Editorial changes to the product information**

An application for a minor editorial change must not be a SRN and the variation requested must not indicate any reduction in the quality, safety or efficacy of the goods for the purposes for which they are to be used (Section 9D(3) of the Act). Review is limited to checking that the proposed editorial change meets the criteria for Minor Editorial Change.

Editorial changes to the PI (not related to safety matters) usually cannot be made by the sponsor without prior approval. Minor editorial changes which may be made by notification include:

- changes to headings to ensure compliance with Appendix 8 to this document;

- relocation of text, without text changes to comply with Appendix 8 to this document;
- deletion of non-marketed presentations or addition of marketed presentations;
- deletion of text that relates solely to deleted indications or non-marketed presentations. However, sponsors do not have the right to delete accompanying texts, for example, precautions;
- *cloning* a PI document to include only marketed dose forms, strengths and pack sizes.

To facilitate a minor editorial change notification, the sponsor must submit to TGA:

- a copy of the approved PI on which the changes have been clearly identified and a clean copy of the amended PI;
- an assurance that no other changes have been made to the PI document and a justification as to why the changes have been made;
- a processing fee<sup>16</sup>.

The TGA must be notified of any minor editorial changes to PI, within 5 working days of their implementation. TGA will acknowledge receipt of the non-safety-related notification, however this does not imply that the text has been reviewed or approved. Any subsequent printed version of the PI must show the date of the TGA approval, if applicable, and the date of the editorial change as *Date of amendment*.

#### **4.4.6 Consumer medicine information**

A Consumer Medicine Information (CMI) must be submitted with all Category 1 and Category 2 applications. Once the CMI has been evaluated by the TGA and the application has been approved, subsequent amendments to the approved PI should be reflected in the CMI, but the CMI is not re-evaluated by the TGA.

A CMI should be submitted with all Category 3 applications that will result in a new ARTG entry, for example, reformulations and new container types.

For information regarding the format and content of the CMI, refer to Schedule 12 of the Regulations<sup>3</sup>.

# 5. 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) <sup>8</sup>. 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, please refer to the TGA website<sup>39</sup>.

Additional Australian administrative requirements are described in *Module 1: Administrative Information and Prescribing Information for Australia*<sup>7</sup>.

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.

## 5.1 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.

## 5.2 Where should applications be 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).

For a Category 3 application send:

- a DSEB Application Form;
- a copy of the letter of application;
- 100% of the relevant evaluation fee.

By post:

The Business Manager  
Financial Services Group  
Therapeutic Goods Administration  
PO Box 100  
Woden ACT 2606  
Australia

Delivery other than by post:

The Business Manager  
Financial Services Group  
Therapeutic Goods Administration  
136 Narrabundah Lane  
Symonston ACT 2609  
Australia

### **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 Category 3 application send:

- a letter of application setting out the reasons for the application;
- relevant administrative information, including a completed DSEB Application Form (Module I);
- documentation (data) supporting the application (Modules 2 and 3).

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.

By post:

The Director  
Drug Safety and Evaluation Branch  
Therapeutic Goods Administration  
PO Box 100  
Woden ACT 2606  
Australia

Delivery other than by post:

The Director  
Drug Safety and Evaluation Branch  
Therapeutic Goods Administration  
136 Narrabundah Lane  
Symonston ACT 2609  
Australia

Historical document

Historical document

**Therapeutic Goods Administration**

PO Box 100 Woden ACT 2606 Australia

Email: [info@tga.gov.au](mailto:info@tga.gov.au) Phone: 02 6232 8444 Fax: 02 6232 8605

**[www.tga.gov.au](http://www.tga.gov.au)**

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