White paper:

How to register a prescription medicine in Australia

Prescription medicines undergo the highest level of regulation of all the medicines regulated by the Therapeutic Goods Administration for supply in the Australian market. This White Paper describes the system and processes for regulatory approval to supply these medicines in Australia.

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Australia's Regulatory System for Prescription Medicines

It is a legal requirement under the Therapeutic Goods Act 1989, that medical products to be imported into, supplied in, or exported from Australia be included in the Australian Register of Therapeutic Goods (ARTG) which is managed by the Therapeutic Goods Administration (TGA).

Prescription medicines are high-risk medicines that contain ingredients that are described in Schedule 4, Schedule 8 or Schedule 9 of the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP) and are available by prescription only. This group of medicines also includes some specified products such as sterile injectables.

The SUSMP lists all the substances, their classifications, labelling and packaging requirements. The classification takes into account a substance's toxicity profile, pattern of use, indications, product formulation and dosage, potential for abuse and need for access.

The table below shows some examples from the SUSMP:

Schedule	Description	Use	Example
4 (S4) Prescription Only Medicine / Prescription Animal Remedy	Prescription only medicines for supply by a pharmacist only.	Therapeutic (drugs)	Amoxicillin, Pneumococcal vaccine
8 (S8) Controlled Drug	Substances that require restriction of manufacture, supply, distribution, possession and use to reduce abuse, misuse and physical or psychological dependence.	Therapeutic (drugs)	Methadone, Morphine
9 (S9) Prohibited Substance	Substances which may be abused or misused; manufacture, possession, sale or use should be prohibited by law except when required for medical or scientific research	Medical or Scientific research	Heroin, coca leaf

In addition to the Therapeutic Goods Administration (TGA), there are four other key roles in Australia's regulatory framework for medicines. These can be separate legal entities or combined. They are:

Who?	Role
Manufacturers	To legally manufacture the medicine in Australia or overseas
Sponsors	Import, export, or manufacture medicines. An Australian manufacturer may also act as a sponsor. Legally accountable for the product quality on the Australian market Must be a resident of Australia or be an incorporated body in Australia with the representative of the company residing in Australia.
Sales organization / Distributers	Distributers can be third-party logistics providers or fourth party logistics providers
Agents	Consultants, such as PharmOut, that act on behalf of manufacturers or sponsors, to register medicines in Australia

Manufacturers

The Therapeutic Goods Act 1989 requires that manufacturers of therapeutic goods hold a licence to manufacture if they engage in any part of the process of producing the medicine or bringing the medicine to their final state, including engaging in the processing, assembling, packaging, labelling, storage, sterilising, testing or releasing for sale of the medicine or of any component or ingredient of the medicine as part of that process. To obtain a licence, a manufacturer must demonstrate compliance with the Australian code of Good Manufacturing Practice (GMP) which describes a set of principles and procedures that when followed, helps ensure that therapeutic goods are of high quality. GMP includes quality management, manufacturing processes, documentation and inspection. The TGA has adopted the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S) Guide to Good Manufacturing Practice for Medicinal Products, as the Manufacturing Principles that are to be applied in the manufacture of therapeutic goods for Australia.

GMP Licence or GMP Clearance?

To obtain a manufacturing licence, manufacturers of medicines must demonstrate compliance with the relevant code of GMP. This is usually, but not always, done through an on-site inspection.

Australian manufacturers must hold a TGA Licence. Fees apply to obtain and maintain licences for Australian manufacturers.

Manufacturers outside Australia must have TGA GMP clearance. GMP clearance letters issued by the Office of Manufacturing Quality (OMQ) of the TGA are required for registration of a new medicine in which overseas manufacturing sites are involved.

An overseas GMP Clearance can be granted by the TGA to a sponsor on the basis of GMP Compliance evidenced by any one of the following:

- A GMP Certificate issued by a country with which Australia has a mutual recognition agreement in relation to the relevant overseas manufacturing site.
- A Compliance Verification assessment of a recent GMP inspection report of the relevant overseas manufacturing site prepared by a competent overseas regulatory agency acceptable to the TGA, together with supporting manufacturing documentation supplied by the sponsor or manufacturer.
- A GMP Certificate issued by the TGA following an on-site audit of the relevant overseas manufacturing site.

The TGA fees for GMP clearance vary with the process required to obtain the evidence of GMP compliance. If an on-site inspection is required, the fees will include travel expenses and an hourly rate of at least $1,220 for 4 to 6 days.

The TGA reserves the right to undertake an inspection of an overseas manufacturing site (with associated fees), irrespective of any other evidence supplied.

Overseas GMP Clearances are granted for a specified time period. Sponsors must monitor the expiry date of GMP Clearances for all overseas manufacturers used and submit further applications with either GMP evidence or a request for a TGA on-site inspection of relevant overseas manufacturing sites before the current GMP Clearance expires.

Applications for a TGA licence or TGA GMP clearance are submitted through the electronic business portal (eBS) on the TGA website. Access to eBS is described under a separate heading below and a summary of the process for GMP approval is depicted in the diagram below.

Onsite inspection for Australian manufacturers or overseas manufacturing sites where TGA approved licenses are not available may take up to 12 months. Final approval of the prescription product application cannot be granted until the appropriate GMP evidence documents are submitted.

Sponsors

The sponsor is responsible for applying to the TGA to have their therapeutic good included on the ARTG. The sponsor must be a resident of Australia or be an incorporated body in Australia and conducting business in Australia where the representative of the company is residing in Australia. The role of the Sponsor in relation to therapeutic goods is defined in the Therapeutic Goods Act 1989 as:

- a person who exports, or arranges the exportation of, the goods from Australia; or
- a person who imports, or arranges the importation of, the goods into Australia; or
- a person who, in Australia, manufactures the goods, or arranges for another person to manufacture the goods, for supply (whether in Australia or elsewhere);

but does not include a person who:

- exports, imports or manufactures the goods; or
- arranges the exportation, importation or manufacture of the goods;
- on behalf of another person who, at the time of the exportation, importation, manufacture or arrangements, is a resident of, or is carrying on business in, Australia.

Once their product is on the ARTG, the sponsor must hold information about ingredients, manufacturing and health benefits of the product, provide information to the TGA about the product on request, comply with advertising requirements, and notify the TGA of any adverse events or problems with the products. To actively monitor for adverse events, management of appropriate pharmacovigilance activities is required.

TGA Departments and Roles

Prescription medicines are assessed as having a higher level of risk and undergo rigorous and detailed assessment by the TGA, with sponsors being required to provide comprehensive safety, quality and efficacy data. The TGA has three major divisions - Market Authorisation Group, Monitoring and Compliance Group and Regulatory Support Group.

Within the Monitoring and Compliance Group, the Office of Manufacturing Quality (OMQ) is responsible for ensuring manufacturers of medicines meet the appropriate standards of quality and are involved in issuing manufacturing licences and GMP clearance.

The Market Authorisation Group (MAG) is responsible for undertaking evaluations of applications to approve new therapeutic products for inclusion on the ARTG, enabling supply in Australia, or export from Australia.

The Office of Scientific Evaluation (OSE) provides scientific advice to support the decisions made by the MAG, which includes evaluation of clinical, toxicological, biological sciences and pharmaceutical chemistry data for therapeutic products.

When making its decisions about the safety of medicines, the TGA uses its own expertise from within the MAG and OSE, and may also seek advice from the Advisory Committee on the Safety of Medicines (ACSOM).

Preparation of the application to the TGA

While the GMP approval is progressing for the manufacture of the product, the next steps involve compiling the documentation in a dossier to demonstrate the quality, safety and efficacy of the product, and the printed materials proposed for marketing the product in Australia.

To assist with preparation of a complete application, TGA has published numerous documents and guidelines on the preparation and submission of prescription medicine applications. In general, the TGA adopt European standards (e.g. pharmacopoeia) and guidelines, but may have adaptations on the European guidelines and separate Therapeutic Goods Orders in place to legislate requirements for specific areas and products. Where a relevant guideline is not met, an appropriate justification must be provided in the dossier. If the requirements of a Therapeutic Goods Order cannot be met, the application must include a request for an exemption from the Therapeutic Goods Act 1989 and a justification for the request.

Where documents to be included in the submission are not originally in English, a copy in the original language and a full translation must be lodged.

If a submitted dossier does not meet the regulatory requirements, it will be considered 'not effective' and will not be accepted for evaluation.

There are two options available for the registration of new prescription medicines which require evaluation of pre-clinical or bioequivalence data and clinical data:

- Category 1 Applications
    - 255 days for evaluation from the date of acceptance
    - Require TGA evaluation of all submitted data for clinical, pre-clinical or bioequivalence information.
- Category 2 applications
    - 175 days for evaluation from the date of acceptance
    - Include submission of two completed evaluation reports from 'acceptable countries' where the product has already been approved. The reports must be independent of each other and the product for supply in Australia must be identical to the product for supply in the countries providing the reports where approval has been granted.

The submission dossiers must be prepared in accordance with common technical document (CTD) format and other TGA regulatory requirements. The TGA is in the process of implementing software to validate, review and process electronic applications for the entry of registered medicines on to the Australian Register of Therapeutic Goods (ARTG). This software can be used for submissions in both electronic Common Technical Document (eCTD) and non eCTD (NeeS) formats. The readiness for eCTD submissions is scheduled for early 2015.

The CTD is a set of specifications for a dossier for the registration of medicines developed by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The CTD provides the framework for the order in which documents must appear in the dossier, organized across 5 modules. The intent of the CTD is to standardise the submissions across all countries, however, the actual content of the dossier for a TGA submission will vary according to the application category and application type, as shown in the document matrix published by the TGA.

The format and content of Module 1 are specific to each country/regulatory agency. The TGA publish guidance on the format and content of Module 1 for Australia, and when each document needs to be provided. For the eCTD Module 1 organisation and content is different and more aligned with international practice.

The format of Modules 2, 3, 4, and 5 is described in the relevant adopted CTD guidelines, with Module 2 consisting of summaries and critical overview on the technical information in Modules 3, 4 and 5. Templates and guidance are available for the format and content of the nonclinical and clinical tabulated summaries in Module 2.

For Module 4 and 5, the TGA accepts three types of applications:

- Conventional applications - containing full study reports of company sponsored studies conducted by them (or on their behalf) that demonstrate safety and efficacy claims
- Literature based submissions - relying solely on bibliographic data to support safety and efficacy claims
- Mixed applications - Mixed applications refer to dossiers where Module 4 and/or 5 consists of a combination of complete study reports of limited nonclinical and/or clinical studies carried out by the applicant and supported with bibliographical references. Mixed applications are treated in the same way as literature-based submissions.

The specific content of Modules 2 to 5 will vary according to the application type and is described in the relevant Australian guidelines, adopted EU guidelines and document matrix available from the TGA website. If an application is submitted that does not follow the recommend guidelines, justifications for not meeting a relevant guideline must be provided. The TGA will assess whether the justification provided:

- clearly identifies the guideline or part of the guideline that is not being met
- specifically addresses why the guideline is not being met
- has a contemporary scientific basis
- includes citations to the relevant reference documents, including TGA documents, where appropriate. Applicants must ensure all such references are included in the dossier.

A summary of the content of each Module is presented in Appendix 1.

The TGA Registration Process

The TGA offer a pre-submission meeting to discuss scientific or procedural issues before formally initiating the submission process. A guideline describes the management and the timing for these meetings which should be well before submission of the pre-planning form or dossier.

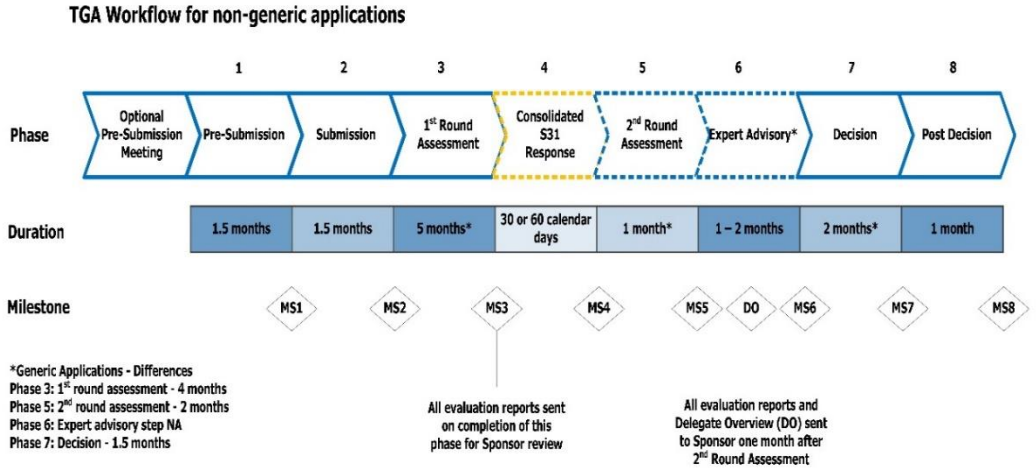
The registration process is designed to take, on average, 330 calendar days (11 months), including the time for applicant activities. The process involves a number of steps with milestones shown in the diagram below.

In the pre-submission planning phase, applicants pay the application fees and lodge details of a proposed application months prior to lodgement of the dossier. An example of the TGA fees for prescription medicine is presented under 'How much does it cost to register a medicine in Australia?'. The pre-submission information allows the TGA to identify milestone dates and plan resource requirements.

- The submission phase concludes when TGA sends the applicant a Planning letter. The TGA Planning letter (issued when a preplanning form (PPF)is considered complete and acceptable) contains:
- the lodgement date for the dossier
- the expected dates for the milestones of the regulatory process
- any issues the TGA has identified when considering the PPF which need to be addressed in the dossier.

In the submission phase, the applicant must lodge a complete dossier. No new data is allowed after the submission date.

Applications must be submitted via the TGA eBusiness Services prescription medicines (PREMIER) electronic lodgement facility (for applications to register a new chemical entity, new fixed combination, similar biological medicinal product or a new generic medicine) or the form Application for the registration, or to vary the conditions of registration, of prescription medicines (all other applications).



How much does it cost to register a medicine in Australia?

The current application and annual fees for registering or listing a medicine on the ARTG are:

Medicine Type	Application Fee* ($AUD)	Annual Charge ($AUD)
Prescription (new chemical entry)	221,400	Biologics 6,585 Non-Biologics 3,955
Prescription (generic)	84,600	Biologics 6,585 Non-Biologics 3,955

*For registration of medicines, the TGA fees include application and evaluation.

Regulation after registration

When you have been successful in obtaining TGA approval for your product based on all the information submitted, there is still more to do. The TGA continue to regulate your product for supply on the Australian market to monitor and evaluate the safety and, in some cases, the efficacy or performance and to manage any risks associated with products.

Once the product is approved for supply, the responsibilities include:

- implementing post-market surveillance systems and adverse event reporting programs which include if your product is supplied in other countries, informing the TGA of any international concerns related to safety or efficacy.
- maintaining an approved TGA risk management plan for the product to identify how safety concerns will be identified and mitigated post-registration.
- updating the information in the TGA submission if there have been any changes to any of the information submitted that may impact safety and efficacy. The TGA publish guidelines on how to manage these changes.
- ensuring that advertising and labelling is performed in accordance with the Therapeutic Goods Advertising Code.
- paying annual fees for registering your product for supply in Australia

References

Therapeutic Goods Administration

www.tga.gov.au

TGA Mandatory requirements for an effective application

http://www.tga.gov.au/industry/pm-argpm-requirements.htm#dossier-content

TGA - Literature based submissions

http://www.tga.gov.au/industry/pm-literature-based-submissions.htm#.U7Xo201-_IU

Therapeutic Goods Act 1989
http://www.comlaw.gov.au/ComLaw/Legislation/ActCompilation1.nsf/0/72D440E51DF66177CA257375000E52B1/$file/TherapeuticGoods1989_WD02_Version2.pdf

Therapeutic Goods Regulations 1990,
http://www.comlaw.gov.au/ComLaw/Legislation/LegislativeInstrumentCompilation1.nsf/0/C85AFC5800F19F8ECA257308002F4D8E/$file/TherapeuticGoodsRegs1990.pdf

Standard for the Uniform Scheduling of Medicines and Poisons No. 1, Poisons Standard

http://www.tga.gov.au/industry/scheduling-poisons-standard.htm#.U6OovvmSwYE

TGA Manufacturing medicines

http://www.tga.gov.au/industry/manuf-medicines.htm#.U8SJ9PmSwYE

GMP clearance for prescription medicines

http://www.tga.gov.au/industry/manuf-pm-gmp-clearance.htm#.U8SKgfmSwYE

TGA structure

http://www.tga.gov.au/about/tga-structure.htm#.U8SK8fmSwYE

Australian regulation of prescription medical products

http://www.tga.gov.au/industry/pm-basics-regulation.htm#.U8SMOvmSwYE

Common Technical Document (CTD)

http://www.tga.gov.au/industry/pm-argpm-ctd.htm#.U8SNGPmSwYE

Australian Regulatory Guidelines for Prescription Medicines (ARGPM)

http://www.tga.gov.au/industry/pm-argpm.htm#.U8SOJPmSwYE

Prescription medicines registration process

http://www.tga.gov.au/industry/pm-argpm-process.htm#.U8SOSPmSwYE

TGA - Australian register of therapeutic goods (ARTG)

https://www.ebs.tga.gov.au/

TGA – Therapeutic goods advertising code

http://www.tga.gov.au/industry/legislation-tgac.htm#.U7XjO_mSxid

TGA eBusiness Services

http://www.tga.gov.au/about/ebs.htm#.U7XkGPmSxid

Ingredients Australian Approved Names List

https://www.ebs.tga.gov.au/

PharmOut website

http://www.pharmout.net/

White Papers http://www.pharmout.net/downloads/index.php

Sources

Links used within this document are prone to change. Please refer to the appropriate source for the most recent information. We endeavour to keep an up-to-date record of information at www.pharmout.net

Appendix 1 Common technical document (CTD) Modules format and content summary

Module 1: Administrative information and prescribing information (not for use with eCTD)

Module	Content
1.0.0	Electronic lodgement cover sheet
1.0.1	Letter of application
1.0.2	Responses to questions for information
1.1	Comprehensive table of contents
1.2.1	Application form
1.2.2	Pre-submission details
1.2.3	Patent certification
1.3.1	Product information and package insert
1.3.2	Consumer medicines information
1.3.3	Human embryo/embryonic stem cell declaration
1.3.4	Label mock-ups and specimens
1.4	Information about experts & expert declarations
1.5.1	Literature-based submission documents
1.5.2	Orphan drug designation
1.5.3	Genetically modified organisms consents
1.5.4	Additional trade name declarations
1.5.5	Co-marketed medicines declarations
1.6	Drug and plasma master files and certificates of suitability
1.7	Good manufacturing practice
1.8	Compliance with meetings and pre-submission processes

1.9	Individual patient data declaration
1.10	Overseas regulatory status
1.11	Summary of biopharmaceutic studies
1.12	References to paediatric development program
1.13	Information relating to pharmacovigilance Risk management plan
Annex I	Antibiotic resistance data
Annex II	Overseas evaluation reports

Module 2: Common technical document summaries

Module	Content
2.1	Common technical document table of contents (Modules 2–5)
2.2	CTD introduction
2.3	Quality overall summary Drug substance Drug Product Facilities and equipment
2.4	Nonclinical overview
2.5	Clinical overview
2.6	Nonclinical written and tabulated summaries Pharmacology Pharmacokinetics Toxicology
2.7	Clinical summary Clinical pharmacology studies Clinical efficacy Clinical safety Literature references

	Synopses of individual studies

Module 3: Quality

Module	Content
3.2.S	Drug Substance
	Manufacturing process- description, controls, validation, development and control of materials
	Structure, characterization (physicochemical and biological)and impurities
	Analytical testing - methods, reference materials, validation, batch analysis
	Container
	Stability – study design, analytical methods and results
3.2.P	Drug Product
	Composition
	Development – components, drug substance, excipients, formulation, overages
	Manufacturing process- description, controls, validation, development
	Structure, characterization
	Control of excipients Control of Drug Product including analytical testing - methods, reference materials, validation, batch analysis
	Container
	Stability- study design, analytical methods and results
3.2.A	Facilities and equipment
	Adventitious agents safety evaluation
	Excipients
3.2.R	Regional information
3.3	Literature references

Module 4: Nonclinical study reports

Module	Content
4.1	Table of contents
4.2.1	Pharmacology
4.2.2	Pharmacokinetics
4.2.3	Toxicology
4.3	Literature references

Module 5: Clinical study reports

Module	Content
5.1	Table of contents
5.2	Tabular listing of all clinical studies
5.3	Clinical study reports
5.3.1	Biopharmaceutic studies
5.3.2	Reports of studies pertinent to pharmacokinetic using human biomaterials
5.3.3	Pharmacokinetic studies
5.3.4	Pharmacodynamic studies
5.3.5	Efficacy and safety studies
5.3.6	Post marketing studies
5.3.7	Case report forms and individual patient data
5.4	Literature references

PharmOut is an international GMP consultancy serving the Pharmaceutical, Medical Device and Veterinary industries. PharmOut specialises in PIC/S, WHO, United States FDA, European EMA, and Australian TGA GMP consulting, engineering, project management, training, validation, continuous improvement and regulatory services.

Our team includes international GMP experts who have previously held leadership roles within regulatory bodies.

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