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OVERVIEW ON REGULATORY REQUIREMENTS FOR REGISTRATION OF PRESCRIPTION MEDICINES (GENERICS) IN AUSTRALIA (TGA)

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ABSTRACT

The Therapeutic Goods Administration (TGA) is a division of the Australian Government Department of Health and Ageing and is responsible for regulating therapeutic goods including medicines, medical devices, blood and blood products. Essentially, any product for which therapeutic claims are made must be listed, registered or included in the Australian Register of Therapeutic Goods (ARTG) before it can be supplied in Australia. Australia's system of drug regulation encompasses two major steps. Medicines must first be entered on the Australian Register of Therapeutic Goods (ARTG) following approval by the Therapeutic Goods Administration (TGA) for acceptable quality, safety and efficacy. The technical data requirements for the registration of medicines evaluated by the Drug safety evaluation board (DSEB) have been closely aligned with those required for applications for marketing authorisation of a medicine published by the European Union (EU). Getting approval for the generic drugs was ambiguous and unorganized till the initiation of streamlined submission process, which is newly introduced approval process for prescription medicines in Australia from November, 2010. By utilizing this process, TGA increased the transparency of evaluation process and well defined timelines have been provided which benefits the pharmaceutical companies in obtaining approval without time delay.

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INTRODUCTION

Therapeutic Goods Administration (TGA) is the regulatory authority for Australia. The objective of the Therapeutic Goods Act 1989 is to provide a national framework for the regulation of therapeutic goods in Australia, so as to ensure their quality, safety, efficacy and timely availability. A key focus of the TGA is to ensure that consumers

have timely access to medicines. This includes ensuring that the necessary evaluation and assessment procedures are conducted to enable consumers access to the latest treatments available which are safe and of good quality.

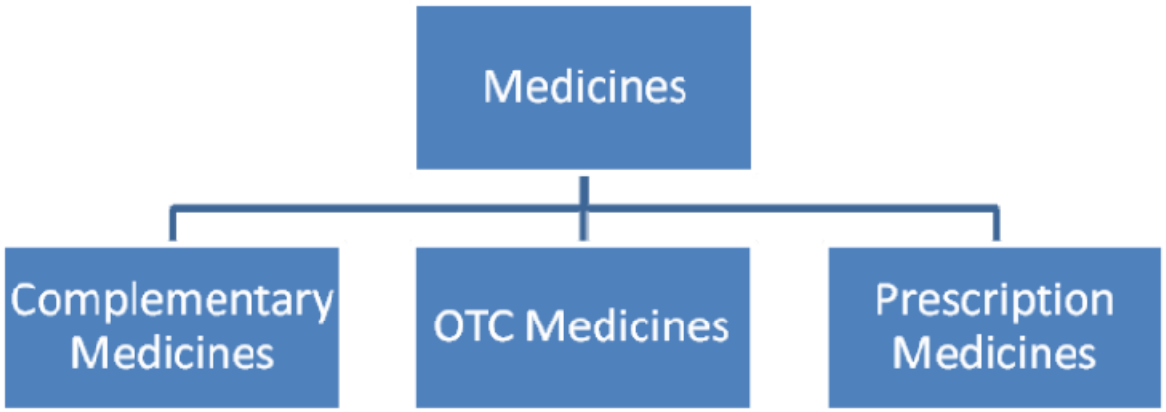
In Australia, medicines can be classified as registered medicines or listed medicines, depending on their ingredients and claims made. Registered medicines can be further classified as non-prescription (low risk) registered medicines and as prescription (high risk) registered medicines. All medicines which are for export only are considered as listed medicines.

The Therapeutic Goods Act 1989 defines a medicine as [12]:

'Therapeutic goods that are represented to achieve, or are likely to achieve, their principal intended action by pharmacological, chemical, immunological or metabolic means in or on the body of a human or animal.' The classification of medicines in Australia was depicted in figure 1.

The TGA categorizes medicines into the following groups for regulatory evaluation:

Figure 1. The classification of medicines in Australia was depicted in [12]



Complementary Medicine:

'Therapeutic goods consisting wholly or principally of one or more designated active ingredients, each of which has a clearly established identity and:
(a) a traditional use; or
(b) any other use prescribed in the regulations.'

OTC Medicine:

An over the counter (OTC) medicine is a therapeutic good mentioned in Part 3 of Schedule 10 of the Therapeutic Goods Act 1989 that does not meet the criteria for mention in Schedule 4, 8 or 9 of the Poisons Standard.

Examples include:

- antiseptics
- sunscreens
- all other therapeutic goods, except for a therapeutic device, not mentioned in another Part of Schedule 10
- an excipient in therapeutic goods mentioned in Schedule 10
- Therapeutic goods referred for evaluation to the Scheduling and Over the Counter Drug Evaluation Section of the TGA.

Prescription Medicine: [12]

Prescription medicines are high-risk medicines that contain ingredients on that are described in Schedule 4, Schedule 8 or Schedule 9 of the Standard for the Uniform Scheduling of Drugs and Poisons (SUSDP) and are available by prescription only. The Drug Safety Evaluation Board (DSEB) evaluates the majority of prescription medicine applications. Examples of prescription medicines are all prescription medicines (e.g. amoxyl) and all injectables (e.g. insulin for diabetics). All prescription medicines must be registered.

Prescription medicines and over-the-counter medicines which meet Australian standards of quality, safety and efficacy are included on the

Australian Register of Therapeutic Goods. Medicines may be registered or listed.

Registered products are thoroughly evaluated and are labelled with an AUST R number. Listed products, such as complementary medicines, do not have to undergo the same assessments and are labelled with an AUST L number. They are not routinely evaluated before marketing, but are subject to a random audit after listing. Some medicines, such as those compounded for individual patients, are not regulated.

AUST R products [10]

Medicines that are registered include:

- ⇨ almost all prescription medicines
- ⇨ a number of products, such as vaccines, which although not classified in law as needing a prescription warrant detailed evaluation
- ⇨ almost all conventional over-the-counter medicines including, for example, packs of aspirin and Paracetamol tablets sold from supermarkets
- ⇨ a very small number of complementary medicines where the TGA has been satisfied that specific claims of efficacy in treatment or prevention of a disease are supported by adequate evidence.

The approval of AUST R products is based on satisfactory assessments of their quality, efficacy and safety.

AUST L products [10]

The group of medicines that are listed consists almost entirely of complementary medicines. These include herbal medicines, most vitamin and mineral supplements, other nutritional supplements, traditional medicines such as Ayurvedic medicines and traditional Chinese medicines, and aromatherapy oils.

AUST L medicines must: not contain substances that are prohibited imports, come from endangered species or be covered by the national regulations which control access to many substances (Standard for the Uniform Scheduling of Drugs and Poisons) conform with lists of permitted ingredients (minerals, vitamins, declared listable substances).

Prescription drug sales in Australia at around US$8 billion constitute a small share of the US$800 billion global market. Yet Australia is a high income economy with strict regulatory requirements closely monitored by drug policy analysts and the pharmaceutical industry. [11]

To get an approval for the generic manufacturer should provide quality data and should demonstrate the bioequivalence of the generic drug product with reference drug product and should submit the dossier in Common technical document (CTD/eCTD) format.

TYPES OF APPLICATIONS [2]

Category 1: New chemical entities, new biological entities, new combination products, extension of indications, major variations, new generics, minor variations.

Evaluation time: 255 working days from the date of acceptance.

Category 2: Applications supported by previous approvals and independent evaluation reports, from two acceptable countries

Evaluation time: 175 working days from the date of acceptance

Category 3: Applications involving changes to the quality data of medicines already included on the ARTG which, in the opinion of the TGA, do not need to be supported by clinical, non-clinical or bioequivalence data.

Evaluation time: 45 days receipt of the application.

The TGA targets the following mean evaluation times, excluding any clock stops to respond to S31 questions, for different types of application: [4]

- 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
- Other Category 1 applications, 130 working days.

Streamlined Submission Process [3]

Streamlined submission process, which is newly, introduced approval process for prescription medicines in Australia by this process, TGA improvised the transparency of approval process and timelines. This process contains seven phases. The implementation of the streamlined submission process is one project within the BPR (Business Process Reform) program. Each month, the BPR update provides information on the progress of PPF (Pre-submission Planning Form) and submissions under the streamlined submission process and other information to assist sponsors with the new requirements.

The key elements of this streamlined process are:

- a pre-submission planning phase where sponsors lodge details of a proposed submission at least 2½ months prior to lodgement of the actual submission and associated dossier
- use of information submitted in the pre-submission phase to identify evaluation resource requirements, timeframes and key milestones for the assessment and determination of the submission
- improved quality of submission dossiers (i.e. prepared in accordance with common technical document (CTD) format and other TGA requirements)
- comprehensive process to check the submission dossier prior to commencement of theevaluation process to ensure compliance with TGA regulatory requirements (i.e. submission is effective)
- implementation of new business processes within the TGA to manage more effectively the workflows associated with submission assessment and determination
- consolidation of regulatory requests issued under S.31 of the *Therapeutic Goods Act 1989* (the Act) at a single stage in the evaluation process and a requirement for sponsors to provide information and documents in response within a defined timeframe.

CRITICAL REQUIREMENTS FOR DOSSIER COMPILATION

- ✓ Quality Requirements
- ✓ Labeling Requirements
- ✓ Bioequivalence studies

Quality Requirements [5]

With regards to quality (Q) data, this type of submission should include at least general information and information related to the starting and raw materials, manufacturing process of the active substance(s), data on characterization of the active substance(s), control of substance(s), and description and composition of the finished medicinal product.

The applicant should provide a statement on the components and composition of the product. This should be followed by information on raw materials (active ingredient and inactive ingredients), description of manufacturing facility, manufacturing process and packaging instructions, in-process information, packaging material controls, controls for finished dosage form, analytical methods for the drug substance and drug product, stability of finished dosage form, and availability of samples. If the generic product is a parenteral product, the applicant must provide sterilization assurance information and data package.

Labeling Requirements [6] & [7]

The Therapeutic Goods Order 69 General requirements for labels for medicines (TGO 69), sets out the legislative general requirements for labels for medicines.

1. Space for the Pharmacist's Label

There should be a clear space for the pharmacist's dispensing label measuring a minimum of 80 x 40 mm. This is the size of the most commonly used computer-printed dispensing label.

Dispensing label:

1. Batch number
2. Expiry date
3. Storage instructions
4. Product name
5. Strength
6. Name of the active ingredient(s)
7. Dose form

8. Barcode (EAN barcode)
9. Signal headings
10. Warning statements
11. AUSTR number

2. Batch Number and Expiry Date

The batch number and expiry date should be positioned together and situated preferably on the end or side panel of the package. The batch number and expiry date should be easily legible; for example ink is preferred over embossing. For eye preparations and other topical, the words "*after opening use within [xx] days*" should be on the label.

3. Storage Conditions

Ideally, the storage conditions should be located close to the batch number and expiry date, and preferably on the front or side panels as end panels are already filled with product / active ingredient names and / or batch expiry information.

4. Barcode

An EAN barcode can be used to facilitate electronic aids in dispensing and as a means of double-checking that this is the correct product to be dispensed. To be effective, it must be located so that it will not be covered by the pharmacist's dispensing label and can still be scanned after the pharmacist has affixed the dispensing label.

5. Product Name and Strength

Both the product name and the active ingredient names and strength should be prominently and equally displayed on the packet on at least three sides, including the two end panels. Strength and quantity should also be displayed.

6. Dose Form

Terminology concerning the long-acting dose forms should be accurate, relate to the product and be clearly specified on the label. For example, extended release, sustained release, controlled release or modified releases are sometimes used.

7. Packaging colour and Design

The use of colour and design should not unnecessarily clutter or obscure the message of the labels but make them clear and distinguishable. Pictures or graphics should be meaningful, appropriate, and represent the use of a medicine, and not suggest an unapproved use. Consideration should be given to including a graphical representation of the tablet on the outer packet.

8. Tamper-evident Packaging

The tamper-evident packaging should not interfere with the ability of the pharmacist to place the dispensing label.

9. Blister packaging

Ideally for blister packaging, each blister cover should include both the active and the product names, and the strength, batch number and expiry date of the medicine. However, this is not always possible. In cases where blisters are small, repetitive diagonal use of product names over the blister covers with expiry date and batch number on the side can assist with identification of partly used packs.

10. Use of product names in other documents

Consumer Medicine Information

The CMI should contain both active and product names at the beginning of the document. Use of product name is only encouraged where information relates to that product of the medicine. Use of active ingredient name for negative information only is not acceptable.

Product Information

The product name should not be used only to present positive information in the product labeling, nor the generic name used to present only negative information associated with the product. The product 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.

Bioequivalence requirements [8]

- ✓ Two medicinal products containing the same active substance are considered bioequivalent if they are pharmaceutically equivalent or pharmaceutical alternatives and their bioavailability (rate and extent) after administration in the same molar dose lie within acceptable predefined limits.

- ✓ In bioequivalence studies, the plasma concentration time curve is generally used to assess the rate and extent of absorption.
- ✓ Selected pharmacokinetic parameters and preset acceptance limits allow the final decision on bioequivalence of the tested products.
- ✓ AUC, the area under the concentration time curve, reflects the extent of exposure. C_{max}, the maximum plasma concentration or peak exposure, and the time to maximum plasma concentration, t_{max}, are parameters that are influenced by absorption rate.

Generic medicinal products:

- ✓ In applications for generic medicinal products according to Directive 2001/83/EC, Article 10(1), the concept of bioequivalence is fundamental.
- ✓ The purpose of establishing bioequivalence is to demonstrate equivalence in biopharmaceutics quality between the generic medicinal product and a reference medicinal product in order to allow bridging of preclinical tests and of clinical trials associated with the reference medicinal product.
- ✓ The different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance are considered to be the same active substance, unless they differ significantly in properties with regard to safety and/or efficacy.

Design, conduct and evaluation of bioequivalence studies:

- ✓ The number of studies and study design depend on the physico-chemical characteristics of the substance, its pharmacokinetic properties and proportionality in composition, and should be justified accordingly.
- ✓ In particular it may be necessary to address the linearity of pharmacokinetics, the need for studies both in fed and fasting state, the need for enantioselective analysis and the possibility of waiver for additional strengths.
- ✓ The study should be designed in such a way that the formulation effect can be distinguished from other effects.

Standard design:

If two formulations are compared, a randomised, two-period, two-sequence single dose crossover design is recommended. The treatment periods should be separated by a wash out period sufficient to ensure that drug concentrations are below the lower limit of bioanalytical quantification in all subjects at the beginning of the second period. Normally at least 5 elimination half-lives are necessary to achieve this.

Alternative designs:

Under certain circumstances, provided the study design and the statistical analyses are scientifically sound, alternative well-established designs could be considered such as parallel design for substances with very long half-life and replicate designs.

e.g. for substances with highly variable pharmacokinetic characteristics.

Test product:

The test product used in the study should be representative of the product to be marketed and this should be discussed and justified by the applicant.

For oral solid forms for systemic action:

The test product should usually originate from a batch of at least 1/10 of production scale or 100,000 units, whichever is greater, unless otherwise justified. The production of batches used should provide a high level of assurance that the product and process will be feasible on an industrial scale. In case of a production batch smaller than 100,000 units, a full production batch will be required. The characterisation and specification of critical quality attributes of the drug product, such as dissolution, should be established from the test batch, i.e. the clinical batch for which bioequivalence has been demonstrated.

Samples of the product from additional pilot and / or full scale production batches, submitted to support the application, should be compared with those of the bioequivalence study test batch, and should show similar in vitro dissolution profiles when employing suitable dissolution test conditions.

Comparative dissolution profile testing should be undertaken on the first three production batches. If full scale production batches are not available at the time of submission, the applicant should not market a batch until comparative dissolution profile testing has been completed.

Selection of the reference product:

The selection of the reference product used in a bioequivalence study should be based on assay content and dissolution data and is the responsibility of the Applicant. Unless otherwise justified, the assayed content of the batch used as test product should not differ more than 5% from that of the batch used as reference product determined with the test procedure proposed for routine quality testing of the test product.

The applicant should document how a representative batch of the reference product with regards to dissolution and assay content has been selected. It is advisable to investigate more than one single batch of the reference product when selecting reference product batch for the bioequivalence study.

SUBMISSION PROCESS PHASES [3]

In general this process contains seven phases.

1. **Pre-submission**
   Sponsors complete and lodge a pre-submission planning form (PPF). The PPF provides information on the scope and scale of a submission, including details of the quality, non-clinical, and clinical evidence. Based on the PPF information, TGA assign resources for the evaluation process. Pre-submission Planning Form should be lodged at least 2 ½ months prior to the intended lodgments date for the submission. Within six weeks of receipt of a Pre-submission planning form, the TGA will send the sponsor a TGA planning letter that provides the expected submission date.
2. **Submission**
   The TGA will send a planning letter to the sponsor, identifying whether the submission is accepted for evaluation. After receipt of the TGA planning letter, lodgment of Submission and supporting data within a month. Sponsors must lodge well-planned, high quality, complete submission dossiers. Sponsors must ensure submissions meet the TGA requirements for format and content.
   Requirements During submission
   Application Fee ($7,600): The Application fee is a proportion of the evaluation fee that is non-reimbursable from the time of submission. Where submissions are not accepted due to deficiencies in the submission this amount will be retained by the TGA, covering administrative costs associated with the Submission phase.
   Evaluation Fee ($100,000): For Category 1 and 2 submissions, payment of 100% of the evaluation fee is required when the submission is lodged.
3. **1st round Assessment**
   The 1st Round Assessment will consider all the supporting data provided with the submission. Where there are issues or questions about any component of the submission a consolidated set of questions from all evaluation areas within the TGA will be developed and sent to the sponsor by a pre-determined date. The default period of 1st Round Assessment is 90 days for completion, with an additional 30 days for the preparation of the consolidated set of questions.
4. **2nd round Assessment**
   Response should be send to TGA by Sponsor within 30days. Responses must be provided in electronic text PDF format. Sponsors should also submit a hard copy of

their response. After the completion of 2nd round assessment, Evaluation Reports sent to sponsor.

5. **Expert advisory meeting**
   The TGA delegate will review the evaluation reports and if required, prepare a Request for ACOPM (Advisory Committee on Prescription Medicines) Advice. A copy of the Request is sent to the sponsor. This phase is not required for Generic submissions.
6. **Decision**
   The TGA delegate will decide whether the submission is to be approved or rejected. Where any outstanding issues may affect the decision, the delegate may liaise directly with the sponsor during this phase before finalising their decision. The delegate will review all documentation associated with the submission and will make an assessment of the risks and benefits. As part of the review, there may be a number of outstanding issues. These may relate to suggestions for revision of the Product Information (PI), Consumer Medicine Information (CMI) or Risk Management Plan (RMP), or may be for general registration details. The delegate may negotiate these issues with the sponsor prior to making a decision.
7. **Post-Decision**
   Any outstanding evaluation payments are finalized (if applicable), relevant documents are published on the TGA website and a new or varied entry is made to the ARTG.
   The timeline of submission phases are clearly specified in table 1.

Table 1. Timelines for submission [12]

PHASE	ACTION	TIMELINE
1.Pre-submission	• Sponsor submits Pre-submission planning Form • TGA Commences processing Pre-submission planning Form • TGA planning letter sent to sponsor	At least 75 days before the submission
2. Submission	• Lodgment of submission and supporting data	------
3. 1st Round assessment	• Commencement of evaluation • A consolidated set of questions is sent to the sponsor	120 days
4. 2nd Round assessment	• Response from Sponsor to TGA • Evaluation Reports sent to sponsor	60 days
5. Expert advisory review	• Request for ACOPM • Planned ACOPM meeting	60 days
6. Decision	• Decision date	30 days
7. Post decision	• Draft AusPAR sent to sponsor • ARTG entry created	30 days

Data evaluation

The data submitted with an application is divided into three types.

- Quality data
  - The composition of the drug substance and the drug product
  - Batch consistency
  - Stability data
  - Sterility data (if applicable)
  - The impurity content

These data are evaluated by chemists, biochemists, microbiologists, toxicologists and others working for the TGA.

- Nonclinical data

- Pharmacology data
- Toxicology data

These data are evaluated by toxicologists.

- Clinical data
- Mostly results of clinical trials

These data are usually evaluated by a medical doctor.

Each data set is evaluated separately, so three evaluation reports are produced. Before the evaluation reports are finalised, the evaluators have the opportunity to ask the sponsor questions about the data submitted. This ability to require the sponsor to provide information is provided by section 31 of the Therapeutic Goods Act 1989. Once completed, the evaluation reports are reviewed internally before they are authorised and sent to the sponsor; the sponsor then has the opportunity to make comments.

The number of copies of modules required by submission type is listed in the below table no. 2.

Table 2.Number of copies of modules required by submission type [13]

Module	Category 1/ category 2 submissions (excluding additional trade names)	Category 1 additional trade name submission	Category 3 submission
Module 1	4	3	1
Module 2	4	0	1
Module 3	2	0	1
Module 4	1	0	0
Module 5	1	0	0

CONCLUSION:

A prescription medication is a licensed medicine that is regulated by legislation to require a medical prescription before it can be obtained. TGA increase the transparency of evaluation process and well defined timelines have been provided which benefits the pharmaceutical companies in obtaining approval without time delay for prescription drugs by implementation of streamlined submission process. In this manuscript the critical requirements and submission process are helpful to understand the regulatory requirements for compilation of dossier for prescription medicines for Australia.

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