Transparent Regulations for Prescription Medicines: The Australian Way

Abstract
The aim of this article is to focus on the regulatory requirements and submission process for prescription generic drugs in Australia. A product for which therapeutic claims are made must be listed, registered or included in the Australian Register of Therapeutic Goods before it can be marketed in Australia. The drug regulatory approval process is complex and resource-intensive. It must be accountable in terms of the quality, safety and efficacy of drugs. This accountability includes an acceptance of a balance between safety and efficacy. There is no such thing as a totally safe drug, and the approval process must recognise the risk/benefit ratio of any particular drug. This requires a detailed evaluation of the data supplied by the sponsoring company. In view of this, TGA increased the transparency of the evaluation process and well-defined timelines which benefited the pharmaceutical companies in obtaining product approvals without any time delay.
Key words: TGA, ARTG, Prescription, Generics.

Introduction

The apex regulatory body for Australia is the Therapeutic Goods Administration (TGA). The Therapeutic Goods Act 1989 provided a national framework for the regulation of therapeutic goods in Australia, so as to ensure their quality, safety, efficacy and timely availability. The TGA ensures that the necessary evaluation and assessment procedures for medicines are conducted to enable consumer's access to the latest treatments which are safe and of good quality in a timely manner.

In Australia, medicines are 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[1].

The Therapeutic Goods Act 1989 defines a medicine as "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."[2]

Classification of Medicines

The TGA categorises medicines into the following groups for regulatory evaluation as shown in Figure 1

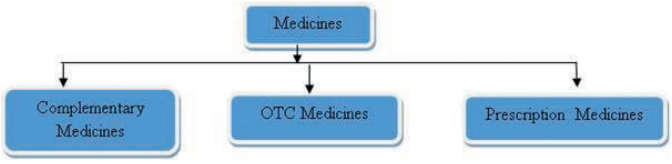

Figure 1: Classification of medicines in Australia

Complementary Medicines

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

OTC Medicines

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 Medicines[3]

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 Drugs and Poisons and are available by prescription only. All prescription medicines must be registered. The Drug Safety Evaluation Board evaluates the majority of prescription medicine applications. Examples include all prescription medicines and all injectables.

For obtaining an approval, the generic manufacturer should provide quality data and should demonstrate the bioequivalence of the generic drug product with reference drug product by submitting the dossier in Common Technical Document (CTD/eCTD) format.

The newly-introduced "Prescription medicines registration process" improved the transparency of the approval process and timelines. The implementation of this submission process is considered one project within the Business Process Reform (BPR) program. Each month, the BPR provides information on the progress of the Pre-submission Planning Form (PPF) and submissions under the prescription medicines registration process and other information to assist sponsors with the new requirements.

Types of Applications[2, 3]

Prescription medicines applications are classified into three categories:

Category 1: Applications for new chemical entities, new biological entities, new combination products, extension of indications, major variations, new generics, minor variations etc. fall under the category 1 application.
Evaluation time: 255 working days from the date of acceptance.

Category 2: Category 2 applications are generally supported by previous approvals and independent evaluation reports, from two acceptable countries.
Evaluation time: 175 working days from the date of acceptance.

Category 3: Category 3 applications involve changes to the quality data of medicines already included on the Australian Register of Therapeutic Goods (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 from receipt of the application.

The TGA targets the following mean evaluation times, excluding any clock stops to respond to S31 questions (consolidated request by the TGA to provide additional information or documents), 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
- Other category 1 applications - 130 working days.

The key elements of this submission process are:

- a pre-submission planning phase, where the sponsor lodges details of a proposed submission at least 2 ¼ 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 CTD format and other TGA requirements)
- comprehensive process to check the submission dossier prior to commencement of the evaluation process to ensure compliance with TGA regulatory requirements (i.e. submission is effective)
- implementation of new business processes within the TGA to manage effectively the workflows associated with submission assessment and determination
- consolidation of regulatory requests issued under S31 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

A. Quality requirements
B. Labelling requirements
C. Bioequivalence studies

A. Quality Requirements[4, 5]
With regard to quality (Q) data, the 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 characterisation 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, 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 sterilisation assurance information and data package.

B. Labelling Requirements[6]
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, the size of commonly used computer-printed dispensing label.
Dispensing label contains batch number, expiry date, storage instructions, product name, strength, name of the active ingredient(s), dose form, barcode (EAN barcode), signal headings, warning statements, 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. For example, ink is preferred over embossing. For eye preparations and other topicals, 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 during dispensing. To be effective, it must be easily 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 and appropriate, and represent the use of a medicine, and not suggest an unapproved use. Consideration should be given to including a graphical representation of dosage form 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 (CMI)
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 labelling, 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.

C. Bioequivalence requirements [7-11]
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.
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. The area under the concentration time curve reflects the extent of exposure. Cmax, the maximum plasma concentration or peak exposure, and the time to maximum plasma concentration, tmax, are parameters that are influenced by absorption rate.

Generic Medicinal Products
The purpose of establishing bioequivalence is to demonstrate equivalence in bio pharmaceutics quality between the generic and 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, and 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 the 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 five 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 1/10th 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 regard 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 [12]

The process of submission is divided into six phases:

Phase 1: Pre-submission

Sponsors complete and lodge a pre-submission planning form. 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, the TGA assign resources for the evaluation process.

The PPF should be lodged at least 2 ¼ months prior to the intended lodgment date for the submission. Within six weeks of receipt of a PPF, the TGA will send the sponsor a TGA planning letter that provides the expected submission date.

Phase 2: Submission

The planning letter sent by the TGA identifies whether the submission is accepted for evaluation. After receipt of the TGA planning letter, lodgment of submission along with supporting data to be done 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

a. Application Fee ($16,600)[13]: 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.
b. Evaluation Fee ($66,000)[13]: For Category 1 and 2 submissions, payment of 100 % of the evaluation fee is required when the submission is lodged.

Table-1: Number of copies of modules required by submission type [14]

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

Phase 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 the 1st round assessment is 90 days for completion, with an additional 30 days for the preparation of the consolidated set of questions.

Phase 4: 2nd round assessment

Responses to questions should be send to the TGA by the sponsor within 30 days. Responses must be provided in electronic text PDF format. Sponsors should also submit a hard copy of their response.

Data evaluation[15]

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

The data submitted will be evaluated by chemists, biochemists, microbiologists, toxicologists and others

working for the TGA.

Non-clinical data
- Pharmacology data
- Toxicology data

Non-clinical data will be evaluated by toxicologists.

Clinical data
- Mostly results of clinical trials

Clinical data are usually evaluated by a medical doctor. Each data set is evaluated separately by three independent evaluators generating three evaluation reports. Before the evaluation reports are finalised, the evaluators may ask the sponsor questions about the data submitted. 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. For generic drug products, expert review may be optional.

Phase 5: 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), 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.

DSEB - Drug Safety Evaluation Board

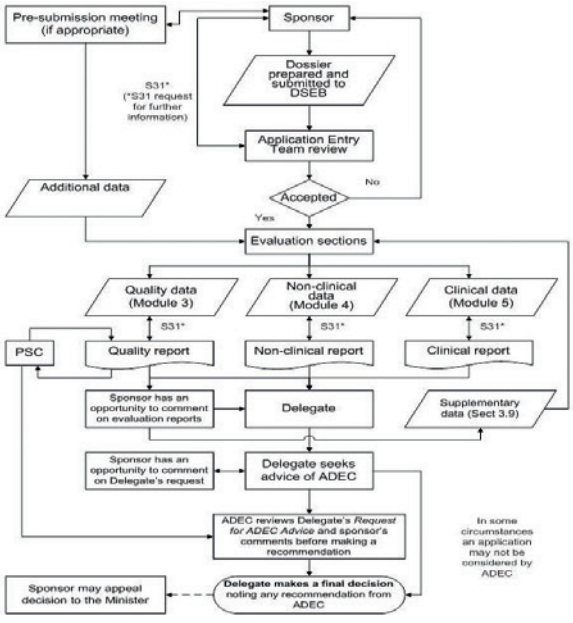

Figure 2: Summary of the evaluation process for category 1 and 2 applications

ADEC - Australian Drug Evaluation Committee
PSC - Pharmaceutical Subcommittee
Source: http://www.tga.gov.au/pdf/archive/pm-argpm.pdf

Phase 6: Post-decision

The Australian public assessment report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve an application. The AusPAR is drafted during the post-decision phase and sent to the applicant for review prior to publication. Any outstanding evaluation payments are finalised (if applicable), relevant documents are published on the TGA website, and a new or varied entry is made to the ARTG.

Table-2: Action plan and timelines for generic application

Phase	Action	Timeline
1.Pre-submission	• Sponsor submits PPF • TGA Commences processing PPF • TGA planning letter sent to sponsor	45 days
2. Submission	• Lodgment of submission and supporting data	45 days
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. Decision	• Decision date	45 days
6. Post decision	• Draft AusPAR sent to sponsor • ARTG entry created	30 days

Table – 3: Comparison of Australian Prescription Medicines Registration Process (New) to Australian Prescription Medicines Streamlined submission Process (old)

Details	Australian Prescription Medicines Registration Process (New)	Australian Prescription Medicines Streamlined submission Process (old)
Pre Submission Planning Form	Defined and available	Not defined
Pre submission meeting	Available	Available
Planning Letter by TGA	Defined and available	Not available
Phases of evaluation	Available	Not available
Notification Letter by TGA	Defined and available	Not available
Section 31 (S31) request	Defined and available	Defined and available
Definite timelines for each phase	Available	Only meets the overall evaluation timeline
Milestone for evaluation in each phase	Available	Not available
Expert review by	Australian Committee on Prescription Medicines (ACPM), pharmaceutical subcommittee (PSC).	Australian Drug Evaluation Committee (ADEC), Pharmaceutical Subcommittee (PSC).
Australian public assessment report (AusPAR)	Defined and available	Not defined

When compared to the Australian Prescription Medicines Streamlined Submission Process (old), the Australian Prescription Medicines Registration Process (New) is divided into phases which have definite timelines and milestones for each phase. These timelines are available to the applicant from the planning letter issued by the TGA.

Conclusion:

Getting approval for generic drugs was ambiguous and unorganised till the initiation of the prescription drug submission process. The TGA increased the transparency of evaluation by providing well-defined process timelines which benefits the pharmaceutical companies in obtaining approval without time delay.

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