Australian regulatory guidelines for OTC medicines
(ARGOM)

July 2003
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.
## Version history

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This is a historic document and is provided for historical reference only. Please refer to the ARGOM for the most current information.
Foreword

Australian Regulatory Guidelines for OTC Medicines

July 2003

These Guidelines describe the information to be supplied with an application for registration of OTC (over-the-counter) medicines in the Australian Register of Therapeutic Goods (ARTG). These medicines will be subject to evaluation by the Non-prescription Medicines Branch of the Therapeutic Goods Administration, in accordance with Section 25 of the Therapeutic Goods Act 1989.

This information will enable the determination of the application for registration and, accordingly, the Guidelines are approved for the purposes of subsection 23(2) of the Therapeutic Goods Act 1989 with effect from 1 July 2003.

The Guidelines also give guidance on the information required to be submitted for consideration of applications to vary information about therapeutic goods included in the Register, which are made under subsection 9D(1), (2) or (3) of the Therapeutic Goods Act 1989.

Terry Slater
National Manager
Therapeutic Goods Administration
(Delegate of the Secretary)
June 2003
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1. Introduction

These guidelines describe the information to be supplied with applications for registration or variation of OTC medicines. These are medicines which are available without a prescription but not 'complementary medicines'. ‘OTC medicine’ and ‘complementary medicines’ are defined in the Therapeutic Goods Regulations 19901.

The object of the guidelines is to assist sponsors to submit applications which will be evaluated in the minimum possible time and be successful.

While the guidelines reflect the views of the TGA and its evaluation committees at the time of publication, there may be occasions where a departure from the guidelines is warranted. If you believe this to be the case, a justification for the departure should be submitted with the application. You may wish to contact staff of the OTC Medicines Section for advice in such instances.

The guidelines contain many references to legislation. However, these references, although accurate at the time of publication, are not intended to be comprehensive. It is the sponsor's responsibility to ensure that current regulatory requirements are fully met.

It is possible for some products containing ‘new’ substances (ie. those not contained in a product currently included in the Australian Register of Therapeutic Goods for supply in Australia) to be evaluated as OTC medicines. Provisional approval of a substance which is not, as yet, included in a product is also possible. Details of provisions for the approval of substances, as opposed to products, are given in Chapter 6B, New substances.

Except where otherwise indicated, these guidelines apply to products rather than substances.

The guidelines are available on the TGA website or in hard copy from the TGA Publications Office. Each chapter is separately numbered to facilitate future additions and amendments.

The TGA would welcome comments or suggestions and these should be directed to:

The Director
Non-prescription Medicines Branch
Therapeutic Goods Administration
PO Box 100
WODEN ACT  2606

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2. Overview

This Chapter gives an overview of the legislative and procedural framework within which OTC medicines are regulated. It also defines the terms used in these guidelines. Information on substances which are not, as yet, included in a product is contained in Chapter 6B, New substances.

Therapeutic Goods

The Therapeutic Goods Act 1989 (the Act) came into operation in February 1991. Its object is:

> to promote the development of a national system of controls relating to the quality, safety, efficacy and timely availability of therapeutic goods used in Australia or exported from Australia, whether the goods are produced in Australia or elsewhere.

'Therapeutic goods' are defined in the Act. All therapeutic goods (other than those which are exempt) must be registered or listed in the Australian Register of Therapeutic Goods (ARTG) before they can be imported, exported, manufactured or supplied in Australia.

Therapeutic goods are divided into ‘medicines’ and ‘medical devices’. Some ‘medicines’ are limited to prescription-only while others are available without a prescription. Non-prescription medicines may be ‘complementary medicines’ or ‘OTC medicines’ and may be ‘listed’ or ‘registered’ in the ARTG.

These guidelines are solely concerned with OTC medicines. Some OTC medicines (eg. sunscreens) are normally ‘listable’ but the majority are ‘registrable’. Information on registration and listing is available on the TGA website 1.

Route of evaluation

Medicines are evaluated by one of three regulatory units. OTC Medicines are evaluated by the OTC Medicines Section (OTC), complementary medicines by the Office of Complementary Medicines (OCM) and prescription and other specified medicines by the Drug Safety and Evaluation Branch (DSEB). The criteria for deciding which of these units evaluates a particular medicine are set out in Schedule 10 to the Therapeutic Goods Regulations.

In some circumstances it may be more appropriate for a particular medicine to be evaluated by a different unit to the one specified in Schedule 10. Here are some examples of where this may occur:

- Where a medicine is currently classified as a 'Prescription Only Medicine' (Schedule 4) but meets the criteria for classification in an OTC schedule and the sponsor intends to lodge an application for down-scheduling;

- Where a product contains a new active substance that is closely related to a substance already classified OTC (eg. an active metabolite of an existing 'Pharmacy Medicine' (Schedule 2) or 'Pharmacist Only Medicine' (Schedule 3) substance) and is likely to meet the criteria for classification as a non-prescription medicine in the Guidelines for the National Drugs and Poisons Schedule Committee2.

The Regulations allow for the transfer of applications between the regulatory units. Once transferred, the applications are dealt with according to the requirements (eg. fees and data requirements) of the new area.

A decision to transfer an application to a different regulatory unit may be taken at the initiative of the TGA delegate (e.g., OTC products containing oral nitrates for the treatment of heart disease are routinely transferred from OTC to DSEB to maintain consistency in evaluation with prescription medicines). In such cases, the sponsor will be advised before the transfer takes place and be given the opportunity to provide comment.

Where a sponsor wishes to have an application dealt with by an evaluation unit other than the one specified in Schedule 10 to the Regulations, they will need to provide a justification to the TGA to establish that this is appropriate. The justification can be provided separately in advance of an application or as part of the application itself.

If the justification is accepted, the application for that product will then be dealt with by the ‘new’ evaluation unit in the same way as other products regulated by that unit (e.g., application and evaluation fees and data requirements will be those of the ‘new’ evaluation unit).

If the justification is refused, any subsequent application for that product will be dealt with according to Schedule 10 to the Regulations. Details of a procedure for appeals are included under Administrative details, below.

The information required in a justification will vary depending on the current and proposed route of evaluation.

**DSEB to OTC or OCM**

Products containing new active substances (i.e., those that are not included in any medicine currently authorised for sale in Australia) are usually evaluated by the DSEB. Exceptions to this general rule are sunscreens (evaluated by OTC) and herbal substances (evaluated by OCM).

Where a justification for evaluation of a product or substance via the OTC or OCM route is proposed, the primary factors to be taken into account include:

- The safety of the active substance;
- The need for professional counselling before use;
- The nature of the ailments or symptoms to be treated (can they be easily recognised by the consumer, do they require medical diagnosis or management?)
- The abuse potential of the product or substance;
- The incidence of adverse effects and contraindications;
- The risk of masking serious disease;
- The risk/benefit profile of the product (e.g., therapeutic index).

Other factors that may be taken into account include:

- Whether the product would be in a lower schedule if presented in a different form (e.g., different pack size, different strength, different indications, different route of administration);
- Whether products containing the substance are available without prescription in other countries with comparable regulatory regimes to Australia;
- Whether the product contains a substance that has a closely related chemical structure and similar therapeutic action to other substances that are in a less restrictive schedule;
- Whether the substance appears to meet the criteria for listing.
OTC to OCM or vice versa

In general, products containing active ingredients that would normally be evaluated as OTC (e.g. paracetamol) in combination with active ingredients that would normally be evaluated as complementary (e.g. herbal substances, vitamins, minerals) will be evaluated via the OTC route.

Where a sponsor wishes to propose a different route to that specified in Schedule 10 to the Regulations, a justification should be provided.

OTC or OCM to DSEB

In some circumstances, sponsors may prefer to have an application evaluated by the DSEB rather than OTC or OCM (e.g. where a product range includes strengths that are ‘prescription’ as well as OTC). A justification should be submitted but minimal supporting data will be required in such cases.

Administrative details

A form (Justification for a particular route of evaluation)³ is provided to assist sponsors in submitting the required information. The justification request should be submitted to the evaluation unit specified in Schedule 10 to the Regulations (e.g. a ‘Prescription Only Medicine’ (Schedule 4) justification request should be submitted to the DSEB) with a copy sent to the proposed evaluation unit. There is no fee for this.

A decision will be made by the TGA within 20 working days (four weeks) of receipt of the justification request. The decision will be made by the relinquishing area following discussion with the proposed receiving area. The sponsor will be advised of the decision by the relinquishing area. If the initial decision is to refuse the justification request, the reasons for refusal will be given.

Following the initial decision, if the sponsor and the TGA cannot come to a mutually acceptable position, the sponsor may request the TGA National Manager to undertake an independent internal review. This review will be completed within 20 working days of the receipt of the request and may involve consultation with the chairs of the relevant evaluation committees.

Excipients

Excipients are usually evaluated via the same route as the products in which they are to be used (e.g. a new excipient that is to be used in complementary medicines will be evaluated by the OCM).

In general, the evaluation criteria for new excipients are common across all areas of the TGA. Information on data requirements is available from the relevant evaluation area.

Currently registered non-prescription transdermal patches

Under Schedule 10 to the Regulations, transdermal systems are routinely evaluated by the DSEB even if they are non-prescription products.

Notwithstanding this, evaluation of a particular application via the OTC or OCM route will be accepted when it involves a change or changes that do not result in a new delivery system or influence the characteristics of the currently approved delivery system. Changes in formulation, membrane or other specific factor(s) that control release of the active frequently result in what could be considered a new delivery system.

Acceptable changes (i.e. to be considered by the OTC or OCM route), therefore include applications involving clinical data, toxicological data, and only those pharmaceutical chemistry changes that do not create a new transdermal system or influence the characteristics of the currently approved system.

Examples of changes that will be accepted for evaluation via the OTC or OCM route are:

• Labelling changes
• Sponsor changes
• Consumer Medicine Information
• Product Information
• Packaging changes, other than immediate packaging
• Product detail changes not involving a change to the delivery system.

Changes other than those specified will require a justification if an alternative evaluation area is desired. For example:
• Product detail changes involving the delivery system (PDF to PMI);
• Quality Control changes – finished product specifications (QFX to QFR) which do not result in a new transdermal system;
• Quality control changes – starting material specifications (QSX to QSS) which do not result in a new transdermal system;
• Manufacturing changes – finished product (MMA to MPR).

The codes quoted above are from the Changes table (Chapter 11).

Relationship to scheduling in the SUSDP

Where a product that contains a new active substance is approved for registration and it appears that the substance meets the criteria for inclusion in a schedule of the SUSDP, the matter will be referred to the National Drugs and Poisons Schedule Committee (NDPSC) for consideration as to the most appropriate schedule for the substance. The sponsor may wish to make a submission to the NDPSC at that time.

Where a product is already included in Schedule 4, 8 or 9 of the SUSDP and the TGA has accepted a justification for evaluation via the non-prescription route, the sponsor should submit an application to the NDPSC for ‘switching’ the substance to a lower schedule. Depending on timeframes, the sponsor should consider submitting these applications concurrently.

In both the above instances, the NDPSC will generally consider the application for scheduling or ‘switching’ schedules after advice of the TGA's decision on registration of the product has been received. The TGA's evaluation report will be made available to the NDPSC to assist in its assessment.

In cases where it is clear that the ‘new’ substance does not meet the criteria for inclusion in any schedule of the SUSDP, the matter will not be referred to the NDPSC.

It must be recognised that the decision on which schedule a substance is allocated is the sole responsibility of the NDPSC. It should not be expected that because a substance or product has been evaluated via the non-prescription route that the NDPSC will necessarily allocate a non-prescription schedule to that substance, or that it will accept a recommendation to include a substance in a particular schedule.

In circumstances where a product is evaluated via a non-prescription route and then the NDPSC allocates or confirms a ‘Prescription Only Medicine’ (Schedule 4) classification, the evaluation will not be repeated via the DSEB.
3. The application

This chapter describes the information required to support an application to register an OTC medicine. In general, that information should consist of an application form (accompanied by the prescribed fee) together with a submission containing information and data to support the product’s registration. Submissions should be page numbered and include an index. Applications prepared in the European or ICH format are preferred.

The application form

The application form is called the New medicine registration application form (OTC). Instructions on how to complete the form are printed opposite the corresponding item in the form. The instructions on the form are additional to the requirements in these guidelines. Contact the OTC Medicines Section if you are unsure as to how to complete any particular item in the form.

Fees

Application and evaluation fees are payable for most applications. Full details of the current fees are contained in Schedule 9 to the Regulations. A summary of fees and charges is available on the TGA website. To avoid delay, you should pay the full application and evaluation fees at the time of submitting your application.

In some circumstances, a waiver or reduction of the evaluation fee (but not the application fee) may be possible under the provisions of Regulation 45 of the Therapeutic Goods Regulations (eg. where the TGA has already evaluated relevant data on a related product and the evaluation can be abridged).

If you believe you are eligible for a waiver or reduction of the evaluation fee, include a request with your application. If approved, a refund will be issued by the Business Management Unit (BMU).

The BMU will acknowledge receipt of your application within a few days of its arrival in the TGA. The acknowledgment letter will quote a TGA Identification Number (TGAIN) which uniquely identifies your application. This number should be quoted in any correspondence or enquires concerning the application.

The submission

In general, a submission for registration of an OTC medicine should include the following components:

- Specifications and stability data as specified in Chapter 4, Quality;
- Copies of all labelling including package inserts;
- A copy of the Product Information (PI) and Consumer Medicine Information (CMI) documents where relevant (refer Chapter 5, Presentation);
- Efficacy and safety information where relevant (refer Chapters 6A, Efficacy and safety and 6B, New substances)


The evaluation process

Instructions for lodging applications are given on the application form. On receipt at the TGA, applications are screened to ensure that they comply with the following criteria:

- correct fees paid;
- form filled correctly;
- all necessary data present (including stability and validation data as detailed in Chapter 4E, Quality – Stability testing);
- all necessary attachments present (eg. labels, PI and CMI documents, where relevant);
- Information on the GMP status of manufacturer(s) provided (usually in the form of a clearance letter from the TGA’s Manufacturer Assessment Section).

If any of these factors are absent, the application may be returned to the sponsor on the basis that “An application is not effective unless: the applicant has delivered … such information … as will allow the determination of the application” (Section 23 of the Act). In such cases the application fee is not eligible for refund but the evaluation fee may be refunded on the basis that evaluation had not commenced.

The sponsor may also be contacted at this stage (before evaluation commences) if, in the opinion of a senior evaluator, the application is unlikely to be approved. In such cases the sponsor will be given the option of withdrawing the application (with loss of the application fee but not the evaluation fee) or requesting that the application proceed regardless.

Applications which are returned at this screening stage or subsequently withdrawn can be corrected and resubmitted (as a new application with the appropriate fees) at any time. The TGA is willing to provide some general guidance as to what would be required for a future application but for detailed or technical assistance, it is recommended that the services of an appropriately qualified and experienced regulatory affairs consultant be sought (see Consultants below).

Where a product is required to be sterile (eg. eye drops), the sterility and preservative efficacy aspects of the product will be evaluated concurrently by the TGA’s Microbiology Section. The microbiology evaluator may contact the sponsor directly if there are any issues relating to this part of the evaluation.

Where a product contains ingredients of animal origin the sponsor must comply with the requirements specified under Ingredients of human or animal origin in Chapter 4B.

Applications for new products may be referred to the Medicines Evaluation Committee (MEC) for assessment and recommendation. However, the delegate may choose to make a decision on the basis of information already to hand without advice from the committee. For example:

- where the new product is a ‘clone’ (ie. identical in all respects except for the name) of an existing evaluated product (with the consent of the sponsor of the ‘parent’ product);
- where the new product is similar to products which have been evaluated in the past (eg. a new brand of paracetamol tablet) and bioequivalence data are not required;
- where all issues have been dealt with by the MEC in the past and the Delegate does not require further advice from the committee.

Applications which are precedential or which contain issues that have not been fully addressed in the past will usually be referred to the MEC.
The MEC comprises members with expertise and experience in medicine, paediatric medicine, clinical pharmacology, pharmacy, toxicology, microbiology, regulatory affairs, pharmaceutical chemistry, manufacturing and forensic pharmacy. Its secretariat is provided by the OTC Medicines Section and meetings are held on a two monthly basis. Further details of the composition and terms of reference of the MEC can be found on the TGA website3.

An evaluation report is prepared by a TGA evaluator for submission to the MEC. The purpose of the evaluation report is to provide an objective regulatory and scientific assessment and summary of the application to assist the committee in reaching a conclusion about the suitability of the product for registration.

Applications for variation of existing products are generally not referred to the MEC unless the advice of the committee is specifically required. Circumstances where this may occur include:

• new indications, directions for use or claims for an existing product;
• a chemistry, quality control or labelling issue which is precedential; or
• where the delegate requires technical or policy advice from the committee.

Where the product is to be referred to the MEC, the sponsor will be sent a copy of the TGA’s evaluation report at least ten days before the cut-off date for the meeting at which the application is to be considered. Comments from the sponsor will be given to the MEC. In general, comments must be limited to three pages and should only address substantial issues raised in the evaluation report. Minor and administrative issues can be dealt with separately by the evaluator. Additional data will not be accepted at this stage.

Where an application is recommended by the MEC for rejection, the committee will usually offer the sponsor the opportunity to appear before a future meeting in support of the application. If the sponsor chooses to accept this invitation, the following considerations will apply:

• The sponsor should contact the OTC Medicines Section as soon as possible to arrange a suitable meeting;
• The sponsor is allocated half an hour (usually towards the end of the meeting) to present their case;
• New data that require evaluation are not usually accepted at this stage;
• Presentation aids (eg. PowerPoint, overhead projector) will be available on request;
• The committee may ask questions at the end of the presentation.

This procedure has been accepted as a long-standing custom of the MEC. It is not a formal appeal and does not affect the sponsor’s appeal rights under Section 60 of the Therapeutic Goods Act 1989. Refer also to Chapter 7, Review of decisions.

‘Clone’ applications

The term ‘clone’ is used in relation to OTC medicines that are identical in all respects to an existing evaluated medicine, apart from the product name and identifying details on the product label.

Where a product is accepted as a ‘clone’, no supporting data are required (apart from the proposed labelling, PI and CMI) and the evaluation fee will be reduced to the amount of the variation evaluation fee.

If the application is approved, the ‘clone’ will be registered in its own right in the ARTG. From the time of registration onwards, the ‘clone’ will bear no legal relationship to the ‘parent’ product. The sponsor of the ‘clone’ will be fully responsible for that product.

In general, ‘clone’ applications must comply with the following requirements:

- The application should be accompanied by a letter from the sponsor of the ‘parent’ product authorising the TGA to access information on the ‘parent’ to support the ‘clone’ application.
- The ‘parent’ product must have been fully evaluated (ie. not a grandfathered product).
- The sponsor must provide an assurance that all quality aspects of the proposed ‘clone’ product are identical to the ‘parent’ product, and that the sponsor will ensure that the ‘clone’ product will comply with all applicable regulatory requirements.
- The application should be accompanied by copies of all labels, PI and CMI (where applicable) of the ‘parent’ product and the ‘clone’.

The TGA will closely compare the labels, PI and CMI of the ‘parent’ and ‘clone’ products. If there are changes beyond the product name and identifying details, the label, PI and CMI will be fully evaluated without regard to the ‘parent’. In such cases, the full new product evaluation fee will apply.

Confidentiality

Applications are treated on a commercial-in-confidence basis. Details of an application will only be discussed with the sponsor or the sponsor’s appointed agent. All TGA committees operate under a strict code of confidentiality. Members of committees must declare any conflict of interest in matters to be considered at a meeting and are excluded from taking part in any final determination of those matters.

The delegate’s decision

The Act is written in terms of two parties – ‘the sponsor’ and ‘the Secretary’. In practice, where the Act specifies that decisions are to be made by ‘the Secretary’, those decisions are usually made by an officer of the TGA to whom the Secretary’s authority has been formally delegated. Delegations of this nature are generally restricted to senior officers.

When an evaluation has been completed, the delegate makes a decision on whether the product is suitable for entry in the ARTG on the basis of the application and accompanying data, advice from evaluation committees, other relevant sources and his or her own professional judgement.

Decisions made under the Act may be appealed – information on appeal rights is given in Chapter 7, Review of decisions.

Entry in the ‘Register’

If your application for registration of a product is approved it will be entered in the Australian Register of Therapeutic Goods (ARTG). You will be sent a letter asking you to check the accuracy of all details of the ARTG entry using your on-line access to the SIME ARTG and confirm it is correct (or advise any amendment required). A certificate of registration will be issued following receipt of your confirmation that all details are correct. The registration of the goods will commence on the day specified for the purpose in the certificate of registration. The goods may not be supplied before this date.

The Certificate of Registration will include a number of conditions of registration. Read the conditions carefully as they must be complied with in order to retain your product in the register.
How long will it take?

The target times for the various types of applications are set out in the table below.

<table>
<thead>
<tr>
<th>Application type</th>
<th>Target time (working days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>New applications</td>
<td></td>
</tr>
<tr>
<td>Variations referred to the MEC</td>
<td>71</td>
</tr>
<tr>
<td>‘Clone’ applications</td>
<td></td>
</tr>
<tr>
<td>Variation processed through TGA only</td>
<td>32</td>
</tr>
<tr>
<td>Variation – notification only</td>
<td>20</td>
</tr>
</tbody>
</table>

These targets are set by agreement between the TGA and industry representative bodies and are exclusive of ‘company response time’ (ie. time taken for the sponsor to respond to issues raised during the evaluation).

The TGA’s goal is to finalise all applications within the target time. To help achieve these goals, the following procedures are followed:

- applications not meeting acceptance criteria (see above) are returned to the sponsor without evaluation;
- where possible, applications are assessed by the evaluator and evaluation committee only once;
- in general, applications are dealt with on the basis of the submitted information – deficiencies can be corrected by the sponsor in a new application rather than by a process of iterative submissions.

Changes to existing products

Specific information on the requirements for changes to existing products is given in Chapter 11, Changes to OTC medicines.

Consultants

Sponsors who are not experienced in preparing registration applications may find it to their advantage to engage the services of an appropriately qualified and experienced regulatory affairs consultant.

Information on how to locate consultants is available on the TGA website⁴.

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4. Quality

This chapter describes the information regarding the quality of the product to be supplied with applications for registration of OTC medicines. It is divided into six sections as follows:

4A Manufacture
4B Formulation
4C Starting material specifications
4D Finished product specifications
4E Stability testing
4F Microbiological testing

In addition to the requirements as detailed in the specific sections, the quality section of the submission should include an overview of the pharmaceutical aspects of the application. This overview should include a development pharmaceutics section as detailed below, and critical summaries of the starting material specifications, the finished product specifications and the stability studies.

The TGA will accept European format Pharmaceutical Expert Reports as an alternative to critical summaries as described in this chapter.

Development pharmaceutics

This section should include a table of the ingredients in the product and their purpose in the formulation (e.g., disintegrant, antimicrobial preservative). Where the use of an overage of an ingredient or a range in the quantity used in batch manufacture is proposed, the reasons for the proposed overage or range should be discussed.

Where a product has modified or unusual drug release characteristics (e.g., sustained release or enteric coated) or an unusual method of manufacture, the 'Development pharmaceutics' section should include a detailed discussion of product development, and the relationship with the finished product specifications where relevant (e.g., the reasons for choosing a particular dissolution test method and limit or the pH dependence of drug release in dissolution testing).

Where a sponsor wishes to obtain approval for a range in the quantity of an ingredient (active or excipient), the 'Development pharmaceutics' section should include details of the reasons for the proposed range(s). The commentary should also refer to supporting validation data where appropriate.
4A. Manufacture

This section provides guidance as to the requirements of the Non-prescription Medicines Branch for the manufacture of OTC medicines and starting materials.

Status of manufacturer – finished product

Where Australian manufacturers are nominated in an application, each manufacturer must be licensed to perform manufacturing of the type proposed. The manufacturer’s licence carries details of the types of manufacture permitted under the licence.

Where a product is imported, each nominated overseas manufacturer is expected to comply with the equivalent standard of good manufacturing practice (GMP) as would be required of an Australian manufacturer. Pre-clearance of overseas manufacturers is strongly recommended.

Details of the information required to establish the standard of an overseas manufacturer are contained in the Standard of Overseas Manufacturers\(^1\). Details of requirements for manufacture are specified in the Australian Code of Good Manufacturing Practice for medicinal products\(^2\) and the EU Guide to GMP for Medicinal Products Annex 1 – Manufacture of Sterile Medicinal Products (available from the TGA Publications Office).

Status of manufacturer – starting materials

For OTC medicines, evidence of licensing or approval of the manufacturer of starting materials is not required.

Where manufacture of a proprietary ingredient is considered a significant step in the manufacture of the finished product (eg. a tablet granulation or excipient pre-mix, or a vehicle for a topical product), evidence of licensing or approval of the manufacturer will be required. GMP evidence is not required where manufacture of a proprietary ingredient is not considered a significant step in finished product manufacture (eg. most colours, printing inks, flavours and fragrances, and proprietary ingredients whose sole purpose is as a source of the preservative system for the finished product).

It is the responsibility of the manufacturer of the product to ensure that the quality of all starting materials is acceptable (Clauses 1.2 and 5.25 to 5.34 of the Australian Code of Good Manufacturing Practice for medicinal products\(^3\) apply).

Manufacturing information

Details of the steps of manufacture should be provided for each manufacturing site. Typically these steps may include manufacture of the dosage form, packaging and labelling, chemical and physical testing, microbiological testing and release for sale. A brief outline of the method of manufacture of the finished product must be included with the application.

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Batch to batch variations in quantities of certain excipients

It is recognised that it may be necessary to vary the quantities of certain excipients from batch to batch in order to achieve acceptable results during the manufacturing process. Changes to the nominal amounts of certain excipients may be made as set out below.

<table>
<thead>
<tr>
<th>#</th>
<th>Excipient type</th>
<th>Acceptable range</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>pH adjusting ingredients</td>
<td>qs</td>
</tr>
<tr>
<td>2</td>
<td>Volume adjusting fluids</td>
<td>qs</td>
</tr>
<tr>
<td>3</td>
<td>Quantity of ingredients whose function is to contribute to viscosity</td>
<td>±10%</td>
</tr>
<tr>
<td>4</td>
<td>Colour in tablet coating (but not in body of tablet)</td>
<td>qs</td>
</tr>
<tr>
<td>5</td>
<td>Solvent in granulating fluid</td>
<td>qs</td>
</tr>
<tr>
<td>6</td>
<td>Granulating fluid (fixed composition)</td>
<td>±10%</td>
</tr>
<tr>
<td>7</td>
<td>Disintegrant (even if the excipient serves more than one role in the formulation)</td>
<td>to +25%</td>
</tr>
<tr>
<td>8</td>
<td>Coating solution</td>
<td>qs*</td>
</tr>
<tr>
<td>9</td>
<td>Talc and water soluble lubricants and glidants</td>
<td>-25% to +100%</td>
</tr>
<tr>
<td>10</td>
<td>Water insoluble lubricants and glidants except talc (eg. magnesium stearate, stearic acid)</td>
<td>±25%</td>
</tr>
<tr>
<td>11</td>
<td>Filler (bulking agent) in hard gelatin capsules</td>
<td>±10%</td>
</tr>
</tbody>
</table>

* Does not apply to modified release products – approval is required for any variation from the registered formulation.

Changes in conformity with the above table will not be regarded as changing the product's registered details and need not be referred to the TGA. It is expected that appropriate validation studies will be performed and that the results will be available on request or during the course of GMP inspections.

Where changes to a product's formulation are proposed which are not included in the table or are beyond the specified range, an application for approval of the change must be made (refer to Chapter 11, Changes to OTC medicines). Once approved, the new formulation details (which may include a range) will be entered in the ARTG.

See also Actives/excipients – variations in weight per batch in Chapter 4B, Formulation.
4B. Formulation

This section provides guidance on the formulation of OTC medicines.

Colouring ingredients

Amended 25 June 2004

All colours contained in medicines for oral use should be included in the list of ‘Colours permitted in medicines for oral use’ on the TGA website¹ (see page 42, Colours permitted in medicines for oral use). This restriction does not apply to dermal products or medicated lipsticks.

Proprietary ingredients

The term ‘proprietary ingredient’ means a formulated ingredient obtained from another manufacturer for which the formulation details are not necessarily known to the sponsor (flavouring and colouring ingredients, for instance, are often sourced as proprietary ingredients).

If a proprietary ingredient is included in your product ensure that either:

• formulation details have already been disclosed to the TGA (in which case you should state the ingredient’s ARTG number in the application form); or

• you have requested the manufacturer of the proprietary ingredient to provide the TGA with details of the formulation on a Notification of a Proprietary Ingredient form, available from the TGA.

If your label contains a negative disclosure (e.g. ‘sugar free’ or ‘alcohol free’), you should also check that the substance is not contained in any proprietary ingredient included in the formulation.

Further information concerning labelling of OTC medicines is given in Chapter 5B, Labelling.

Ingredients of human or animal origin

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

The TGA Approach to minimising the risk of exposure to Transmissible Spongiform Encephalopathies (TSEs) through medicines and medical devices can be found on the TGA website². The TGA has adopted the European Agency for the Evaluation of Medicinal Products (EMEA) Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via medicinal products³, EMEA 410/01 and its subsequent revisions. In this guideline, ruminant materials (bovine, ovine, caprine or cervid) are classified into the following risk categories according to infectivity studies.

EMEA risk categories of ruminant tissues and fluids

Category 1 materials (high infectivity):

Brain, Spinal Cord, Eye

Category II (medium infectivity):

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¹ http://www.tga.gov.au/industry/cm-colourings-oral-use.htm
Ileum, lymph nodes, proximal colon, spleen, tonsil, dura mater, pineal gland, placenta, cerebrospinal fluid, pituitary gland, adrenal gland

**Category III** (low infectivity):
Distal colon, nasal mucosa, peripheral nerves, bone marrow, liver, lung, pancreas, thymus

**Category IV** (no detectable infectivity):
Blood clot, faeces, heart, kidney, mammary gland, milk, ovary, saliva, salivary gland, seminal vesicle, serum*, skeletal muscle#, testis, thyroid, uterus, foetal tissue, bile, bone, cartilaginous tissue, connective tissue, hair, skin, urine

**Notes:**
* Recently, foetal bovine serum (FBS) was considered as a potential risk in vaccines and regulatory authorities around the world took action to ensure that currently available vaccines are manufactured using FBS sourced from BSE-free countries. Whilst serum is considered as Category IV, there is preliminary experimental evidence (Houston F et al, 2000) indicating that blood (therefore serum/plasma) may be infectious.

# Accumulation of the disease-causing prion isoform in skeletal muscle was demonstrated following intramuscular inoculation of mice with scrapie-infected tissue (Bosque PJ et al, 2002).

If any product either contains or is manufactured using ruminant materials or reagents classified by the EMEA as Category I, II or III, a clearance certificate must be issued by the TGA Laboratories Branch (TGAL). TGAL approval may be sought prior to, or in parallel with, the registration application.

Applications for clearance of ingredients of animal origin should be directed to:

The Director
TGA Laboratories Branch
Therapeutic Goods Administration
PO Box 100
WODEN ACT 2606

Provide initial information concerning:
- the product's identification;
- the name of the ingredient(s) of animal origin;
- any pharmacopoeial reference applicable to the ingredient;
- the quantity of the ingredient per dose unit;
- the name of the animal species;
- the name of the body part;
- the country of origin of the animal;
- the health status of animals (animals must have been veterinary inspected and found to satisfy the health requirements for human consumption)

This information will enable TGAL to determine whether any more information is required. If the screening demonstrates that the product could pose a risk of infectious disease transmission, details of additional data requirements will be advised.
Category IV ruminant materials are subject to the TGA Supplementary requirements for therapeutic goods for minimising the risk of transmitting Transmissible Spongiform Encephalopathies (TSEs)\(^4\). Sponsors must self-assess Category IV materials according to the requirements. A questionnaire has been provided to aid sponsors in obtaining information from suppliers\(^5\).

If the material is of human origin you should first contact the Head of TGA’s Immunology Section for details of data requirements. Any material of animal (ruminant) origin which is not highly processed (eg. blood, enzymes) should be submitted to TGA for pre-clearance.

**Modified release products**

Modified release oral dosage forms may be appropriate where:

- the active ingredient has rapid absorption and elimination (eg. half-life of less than 6 to 8 hours) associated with a correspondingly rapid loss of clinical effect;
- the site of absorption is not confined to a limited region of the gastrointestinal tract;
- the product is intended for use in conditions of sufficient duration to warrant the use of a sustained release formulation; and
- the product is able to provide therapeutically effective doses of the active ingredient throughout the dosage interval.

Applications for registration of modified release formulations must be accompanied by evidence to demonstrate that ‘dose-dumping’ cannot occur and that the product meets controlled release claims. The evidence should include clinical data to demonstrate the product’s bioavailability and pharmacokinetics.

Generally, the following bioavailability studies would be appropriate, depending on the product type:

- studies comparing a single dose of the modified release product with a registered conventional release product;
- studies comparing the steady state profile of the modified release product under the proposed dosage regime with that of a registered conventional release product under the approved dosage regime; and
- studies comparing a single dose of the modified release product taken in a fasted state with the same product taken with food (preferably a high fat meal).

In some circumstances, bioavailability studies comparing the proposed formulation with an already registered modified release product may be appropriate, either in addition to the comparison with a conventional release product, or instead of these studies.

If you believe a particular application warrants a departure from this guideline, submit a full justification for the departure with the application.

Information concerning different types of modified release tablets and capsules is given in TGO 56 (General standard for tablets, pills and capsules)\(^6\) – see Clause 2 (Interpretation) and the Supplementary notes.

Multicomponent products

A product may contain two or more active ingredients provided that:

- each active ingredient makes a contribution to the claimed indications;
- the effect of combining the active ingredients in one product does not decrease the safety or efficacy of the product; and
- the product provides rational concurrent therapy for a significant proportion of the target population.

Multi-component products that have the same actives as an existing evaluated product will usually not require efficacy or safety data. Where new combinations are proposed (in respect of the actives present and/or strengths), the safety and efficacy of the combination will need to be justified. Clinical and/or pharmacokinetic data comparing the proposed product with the active ingredients used separately will usually be required to support the efficacy and safety of the proposed combination.

Expert reports and summaries will not be counted in the clinical data pages and may be attached to the cover letter or included with the relevant data.

Overages

If overages are used during manufacture (i.e. where the amount of an ingredient added during manufacture is greater than that nominated in the product's formulation), include details of the overage used.

The 'Development Pharmaceutics' section of the application should include a justification for the proposed overage. Any assay limits which are unusually wide as a consequence of the proposed overage should also be discussed. Details of some commonly applied assay limits are included in Chapter 4D, Finished product specifications (under Further considerations).

Note that overages are not to be stated in the formulation details section of the application form.

Reformulation of existing products

Where a new reformulated product is to replace an existing product, the changes should be identified and a statement of the reasons for the reformulation included. The application should also include a table comparing the old and new formulations.

Actives/excipients – variations in weight per batch

For some substances, the weight of raw material drug used in a batch may vary according to its moisture content and in some cases, according to its potency.

Generally speaking, batch to batch differences in moisture content will be reduced when granules are dried to a constant level of hydration so that the proportions of excipients will remain reasonably constant from batch to batch.

However, where potency varies, the fluctuations in quantity of raw material may affect the proportions of excipients present in the finished product relative to the nominal formula. In some situations, the manufacturer may opt to compensate for the fluctuations in the weight of raw material active added by adjusting the amount of a nominated excipient in order to maintain a target weight for the batch. Such variation will be taken into account during the evaluation and separate batch-to-batch approval is not required.
However, the formulation given in the application should have an annotation indicating that the actual weight of active substance will be varied according to (as appropriate) estimated potency and/or water content and a formula should be provided showing how the amount of adjustment will be calculated. There should be an indication of which other excipients will be varied correspondingly, if any, and within what limits.

The reasons for proposed range(s) in the quantities of any ingredients should be discussed in the ‘Development Pharmaceutics’ section. Validation data should be provided in support of any unusually wide range(s) (i.e. a range wider than that allowed under Batch to batch variations in quantities of certain excipients in Chapter 4A, Manufacture, or a range for a class of excipient not included under Batch to batch variations in quantities of certain excipients).

Validation data may be generated using ‘side batches’ (small scale batches or modified portions of production batches) with the formulation or properties (e.g. pH) at the extremes of the proposed range. Validation data may include:

- compliance with the finished product specifications;
- stability data;
- in some circumstances, comparative dissolution profiles may also be appropriate.

Further information is included under Batch to batch variations in quantities of certain excipients in Chapter 4A, Manufacture.
4C. Starting material specifications

General principles

Applications to register OTC medicines should include information concerning specifications for all ingredients. The term 'starting materials' (also called ingredients or raw materials) includes active substances, excipients, proprietary ingredients and solvents lost by evaporation during manufacture. In all cases, the specifications must characterise the substance and ensure that all batches are of suitable and consistent quality for use in finished product manufacture.

Critical summary of starting material specifications

A critical summary should be provided of the specifications applied to each ingredient (active substances, excipients and proprietary ingredients). Where all of the tests, limits and test methods are of either a BP/Ph. Eur. or USP/NF monograph (and none of the compendial tests has been deleted) this should be stated.

Where non-pharmacopoeial specifications are applied, a brief list of the tests, test methods and limits should be provided (eg. assay (non aqueous titrimetry): 99.0 101.0%). The specifications applied should be justified in respect of their ability to assure the quality and consistency of the ingredients used. Similarly, where a pharmacopoeial monograph is used as the specification, the deletion or modification of pharmacopoeial tests, test methods or limits should be justified.

Pharmacopoeial monographs vs company specifications for starting materials

Generally, it is acceptable to adopt the tests, limits and test methods of either a relevant British Pharmacopoeia (BP), European Pharmacopoeia (Ph. Eur.) or US Pharmacopeia/National Formulary (USP/NF) monograph as the specification for a substance. Where a sponsor wishes to do this, it would be sufficient to state that this is the case. However, it is generally not acceptable to:

- adopt only some of the tests from a pharmacopoeial monograph; or
- selectively combine some tests and/or limits from the relevant BP monograph with some tests and/or limits from the USP monograph (without having ensured full compliance with either one or the other monograph).

Where a sponsor applies pharmacopoeial limits but wishes to use different test methods this should be stated and full details of the test methods should be provided (especially in respect of related substances tests). This will permit the TGA to assess whether the in-house and compendial methods are equivalent and/or whether the modified specifications ensure the overall quality of the substance.

Where there is no pharmacopoeial monograph or sponsors, for whatever reason, wish to use their own in-house specifications, full details of the limits and test methods should be provided for evaluation. In proposing tests and limits, sponsors should note the requirements given in pharmacopoeial monographs for similar substances.
Solvent/Sterilant Residues

Where any of the following substances are used as sterilants or as reaction or recrystallisation solvents in the terminal synthetic steps for an ingredient, the following limits should be applied except in unusual circumstances:

- chloroform not more than 50 ppm
- dichloromethane not more than 100 ppm
- 1,4-dioxane not more than 100 ppm
- trichloroethylene not more than 100 ppm
- ethylene chlorohydrin not more than 50 ppm
- ethylene oxide not more than 1 ppm

Attention is drawn to the BP Supplementary Chapter IV D (Residual Solvents), which includes information concerning solvent residues as well as limits on solvent residues which are more wide ranging than those discussed above. Solvents in Class 1 should not be employed in the manufacture of active substances, excipients, and medicinal products. However, if their use is unavoidable, their levels should be restricted as shown in Table 1 (Class 1 solvents in pharmaceutical products (solvents that should be avoided)), unless otherwise justified.

Single-component non-pharmacopoeial starting materials

Specifications for starting materials which essentially consist of one component would typically include tests and limits for:

- appearance/description;
- identification;
- content/assay; and
- impurities (eg. water, residual solvents, loss on drying, sulfated ash, heavy metals, synthetic impurities and degradants).

Tests for the presence or the proportion of isomers, optical rotation, microbial contamination, particle size distribution, and the clarity, colour and pH of solutions may also be relevant.

Intrinsic mixtures

Substances which are intrinsically mixtures (for example, synthetic polymers or fatty acid esters of glycerol, where mono, di, and triacyl glycerol species are present and where a range of different fatty acid residues is also present eg. surfactants) may require additional tests which control the composition of the mixture such as:

- acid value;
- iodine value;
- saponification value;
• viscosity;
• density; and
• refractive index.

Proprietary ingredients

The specifications applied to proprietary ingredients should be appropriate for the nature of the ingredient, its function in the finished product and its proportion in the finished product.

For example, for a perfume which is a minor component in a liquid or semi-solid product, it may be appropriate to have tests for:
• description (odour, colour, general appearance);
• refractive index or density; and
• prominent peaks in a GC or HPLC trace, or major spots in a thin layer chromatogram.

For an ingredient blend which contains the active substance (for a tablet or capsule, for example) it may be appropriate to include tests for:
• identification of the active;
• content of the active; and
• impurity tests.

Starting materials – additional considerations

The specifications for active ingredients, for which there is no BP/Ph. Eur. or USP/NF monograph, should include tests and limits for related substances (synthetic impurities and degradants). The related substance limits should be proposed after consideration of the:
• toxicology of the impurity and the active ingredient itself;
• route of administration;
• daily dose;
• target population (e.g. children or the elderly); and
• duration of therapy and the proposed indications.

In general, the following limits on impurities will not need to be supported by a detailed justification:

<table>
<thead>
<tr>
<th>Impurities</th>
<th>Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individual identified impurities</td>
<td>not more than 0.5 %</td>
</tr>
<tr>
<td>Individual unidentified impurities</td>
<td>not more than 0.1 %</td>
</tr>
<tr>
<td>Total impurities</td>
<td>not more than 1.0 %</td>
</tr>
</tbody>
</table>
Colours permitted in medicines for oral use

Guideline amended 25 June 2004

A list of colours permitted in medicines for oral use, together with applicable raw material specifications, is included on the TGA website. Indicative data requirements for the evaluation of new colours for inclusion in medicines for oral use are also provided.

1 http://www.tga.gov.au/industry/cm-colourings-oral-use.htm
4D. Finished product specifications

This section provides guidance on specifications that apply to the finished product at batch release and at expiry.

General principles

The finished product specifications are a set of tests and limits which are applied to the product in order to ensure that every batch is of satisfactory and consistent quality throughout its shelf life. The specifications should monitor all parameters (generally by physicochemical testing) where variation would be likely to affect the safety or efficacy of the product. Batch release testing, which is the responsibility of the sponsor, is usually performed on every batch whereas shelf life testing may be performed by the TGA Laboratories throughout the batch shelf life (as part of a routine sampling program or in response to complaints).

Critical summary of the finished product specifications

The suitability of the tests, limits and test methods proposed for the finished product should be discussed with reference to the results of the method validation studies and the ability of the specifications to guarantee the quality and consistency of the finished product. A detailed commentary or justification for any unusual features in the finished product specifications should be included.

A brief list of the tests, test methods and limits should be provided (e.g. assay (capillary GC): 95.0-105.0%). For dissolution tests, brief details of the apparatus, medium and limit should be provided (e.g. dissolution (paddle at 50 rpm, 900 mL of water, Q=80% at 30 minutes)). The summary list should give details of both the batch release and expiry specifications. Where the expiry specifications differ from the batch release specifications, this should be noted. The specification code number and date should be stated.

The limits applied at batch release should be discussed in terms of their ability to ensure that the product will remain within the expiry specification throughout the product shelf life. Any changes or unusual variability in the results obtained in the stability studies require comment in this respect.

Further considerations

Your application should include a copy of the batch release and expiry specifications. Where the tests and limits applied at batch release and at expiry differ this must be clearly indicated. Where analytical test methods in the finished product specifications differ from those used for stability testing, validation data should also be provided for those test methods (where applicable).

Usually, tighter limits are applied at batch release to critical parameters to allow for analytical error during batch release testing and to allow for possible changes to the product during storage (e.g. decomposition of the active). The batch release limits must be chosen in order to guarantee that all batches will comply with the expiry specifications throughout the product’s shelf life.

The expiry specifications should include all of the tests which are included in the batch release specifications. (It is not sufficient to provide the stability specifications alone as they generally do not include a complete set of tests.)
The specifications must include the requirements listed in any relevant Therapeutic Goods Order (eg. TGO 56).

Where your product is subject to a monograph in the *British Pharmacopoeia* (BP), the expiry specifications must include all of the tests and limits in that monograph. However, if you consider that the test method used by the BP is unsatisfactory for your product, you should substitute another method which has been validated.

If there is no BP monograph for your product, the specifications must include all of the requirements in the BP General Monographs (for dosage forms). You should also check the BP and the United States Pharmacopeia/National Formulary (USP/NF) for monographs for similar products to determine appropriate tests and limits to include in the specifications.

Any expiry limits which are less stringent than those commonly applied to the relevant dosage form should be justified in detail. (Note: TGO 56 allows wider limits for content of some active ingredients.) Some commonly applied expiry limits are:

**Content of active ingredient(s)**

- in tablets and capsules 92.5 - 107.5% of stated content
- in creams and ointments 90.0 - 110.0% of stated content
- in oral liquids 90.0 - 110.0% of stated content

**Content of preservative(s) present as excipients**

- antimicrobial upper limit 120% of stated content  
  lower limit – sufficient to be effective
- antioxidant upper limit 120% of stated content  
  lower limit – sufficient to be effective

The specifications for finished products which may reasonably be expected to contain significant quantities of ethylene oxide or ethylene chlorohydrin should include the following limits:

- Ethylene oxide not more than 1 microgram per gram
- Ethylene chlorohydrin not more than 50 micrograms per gram

Where the BP or USP has stricter specific requirements, these should take precedence.

**Impurity requirements for non-pharmacopoeial products**

The specifications for finished products, for which there is neither a BP nor USP/NF monograph, nor a monograph for a closely related finished product, should include tests and limits for substances related to the active ingredient (synthetic impurities and degradants).

In relation to impurity limits, the results of stability studies should be taken into account and reference should be made to information on toxicity.

Unless otherwise agreed in relation to a particular product, limits on impurities in finished products apply to impurities from all sources except water.
In general, the following limits on impurities will not need to be supported by a detailed justification:

- Individual impurities not more than 1% (relative to the active)
- Total impurities not more than 3% (relative to the active)

There may be some drug substances for which lower limits on impurities are appropriate.

An alternative approach to the control of impurities, to that outlined above, is given in the EU documents, Note for guidance on impurities testing: Impurities in new drug substances (CPMP/ICH/2737/99)¹ and Impurities in New Active Substances (3AQ12a)². Sponsors may choose to submit applications which reflect this alternative approach.

Sponsors’ attention is also drawn to the BP Supplementary Chapter IV D (Residual Solvents) which includes information concerning solvent residues including limits on solvent residues. Sponsors should ensure that no ‘Class 1’ solvents have been used in the manufacture of the finished product.

For products which have more than one active ingredient, the limits on impurities associated with one active would usually be determined separately from the limits for impurities associated with the other active(s). In such cases, the limit on an impurity should usually be expressed relative to the content of the relevant active ingredient.

During the testing of finished products, the TGA Laboratories will consider a sample to have failed if it contains a level of impurities greater than the above general limits unless:

- the product is closely related to a product which is subject to a BP or USP monograph which allows a greater content than nominated above; or
- a higher level has been agreed during the process of evaluation for registration; or
- the sponsor can justify the level which has been found in the terms outlined above.

**Tablets and capsules**

If your product is in tablet or capsule form you should ensure that it complies with the relevant Therapeutic Goods Order or BP monograph (requirements of Therapeutic Goods Orders take precedence over those of the BP). Where this is the case, the finished product specifications must include details of any required test (eg. disintegration), referencing the test limits and test method defined in the Order or monograph.

Dissolution testing may be more appropriate than disintegration testing. Modified release products nearly always include dissolution testing in the finished product specification. If you wish to substitute a dissolution test for the BP disintegration test (see point 8, page 16 of the Therapeutic Goods Order No. 56³), the proposed dissolution requirements will need to be evaluated by the TGA in terms of the dissolution apparatus, the rotational speed, the dissolution medium and the sampling time and limit (USP/NF ‘Q’ value preferred). A brief commentary on the proposed test and limit should be included in the ‘Development Pharmaceutics’ section of the submission.

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Microbiological requirements

Sterile products

The official requirements for sterility tests in Australia are those specified in the current gazetted edition of the *British Pharmacopoeia*. This is the minimum standard with which manufacturers must comply. The sterility tests published in editions of the BP and Ph. Eur. prior to 1998 are not acceptable. The *TGA guidelines for sterility testing of therapeutic goods* provide guidance for sterility testing of sterile therapeutic goods supplied in Australia for human use. These guidelines, however, are not mandatory for industry.

Non-sterile products

The *Guidelines for assessing the results of microbiological tests on non-sterile OTC medicines* (Chapter 4F) set out microbial limits which apply to non-sterile dosage forms.

All non-sterile dosage forms should include limits for microbial content in the finished product batch release and expiry specifications. Microbial specifications for solid oral or dry powder products may not be necessary if it can be justified in the application by establishing during product development that the product is at a very low risk of contamination and microbial growth is not supported. It is not a requirement that every batch of a product be tested at batch release. Once it has been demonstrated that the manufacturing processes do not permit contamination by excessive numbers of microorganisms, by testing a number of routine production batches to establish a product history, testing could be reduced to once every 6 to 12 months or on a selected basis (eg. every tenth batch).

Products with a significant water content (eg. creams, gels and oral liquids) are likely to support microbial growth. Such products should include tests and limits for microbial content in both the batch release and expiry specifications. In addition, for products containing an antimicrobial preservative(s), both the batch release and expiry specifications should include physicochemical tests and limits for content of preservatives. Given that the effectiveness of many preservatives is pH dependent, the specifications for such products should usually include requirements for pH which will ensure preservative efficacy.

Product modifications

Sponsors may not implement changes to pharmaceutical data for registered products without prior approval from the TGA, except in accordance with Chapter 11, *Changes to OTC medicines*, and then only in accordance with the specified conditions.

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4E. Stability testing

Reference to prescription medicine guidelines corrected 28 June 2006

Full details of stability testing conducted on the product together with associated validation must be included in the submission. This section provides guidance as to the design, conduct and reporting of stability studies for OTC medicines.

The guidelines are based on the principles and requirements set out in Guidelines on the stability testing of pharmaceuticals, included as Appendix 14 to the Australian regulatory guidelines for prescription medicines (ARGPM) 1.

Departure from the principles set out in this document will only be considered when adequately justified.

General principles

The objective of a stability study is to determine the time during which a pharmaceutical product meets appropriate standards when stored under defined conditions. The product must be shown to remain, or is likely to remain, within its expiry specifications throughout the proposed shelf life when stored under the proposed storage conditions. Thus the difference between release and expiry specifications must take into account the results of stability testing.

Critical summary of the stability studies

In addition to providing full details of the stability studies undertaken in support of registration of a product, a separate critical analysis of each study should be provided. Each of the points listed below should be addressed separately for each stability study.

- A table giving batch numbers, batch types (pilot or production), batch size or scale, storage conditions (temperature, humidity, lighting conditions, and storage upright or inverted for liquids), and storage durations. If the storage conditions were not controlled, this should be stated.

- A statement whether all (or some) of the batches tested were identical with the product intended for marketing in terms of formulation and container (if not, the differences should be justified and full details provided).

- A statement whether the method of manufacture and manufacturing equipment for the batches tested were identical with the product intended for marketing (If not, the differences should be justified and full details provided).

- Brief details of the results observed for each of the test parameters included in the studies, as follows. Separate comments should be provided for each test parameter.

  - a heading (parameter/test name, limits, and test technique) eg. Content of salicylic acid (HPLC - NMT 0.3%)

  - an assessment and interpretation of the trends observed in the results of testing (numerical description preferred), the variability in the results, and any anomalous results (anomalous results and unusual variability in the results should be discussed) – if excessive variability in the results prevent assessment of the trends, this should be stated.

1 http://www.tga.gov.au/industry/pm-argpm.htm
• State for which of the test methods, used in the studies, validation data have been provided in the dossier (all assay methods should be validated and stability-indicating).

• Any change in test methods while the studies are in progress should be justified.

• The basis for selecting the proposed shelf life and storage condition should be discussed.

Where a sponsor applies to extend the shelf life of an already registered product, the critical summary should state whether stability studies for the product have previously been evaluated by the TGA. If this is the case, the summary should:

• provide details of the date of the approval letter as well as file and reference numbers (including the TGAIN); and

• state whether the stability data provided are a continuation of studies previously evaluated by the TGA (ie. an extension of a study using the same batches, storage conditions and test methods).

Sponsors may choose the format for the critical summary of the stability data. The following headings may be appropriate:

• Study design

• Test methods

• Commentary on the results obtained in the studies for individual parameters (including any trends)

• Conclusions and summary of claims.

**Stability data requirements**

**Active raw material**

Stability data should be provided for an active raw material which is a new chemical entity. While not mandatory for existing OTC active substances, inclusion of such information with an application may provide a useful guide to the problems which may be encountered during stability studies on finished products.

**Finished product**

At the time of submission, the data package should include sufficient stability data to justify a shelf life of at least 12 months. This requires studies in which satisfactory results have been obtained under the following duration and conditions of storage:

• 12 month duration with storage at the proposed maximum storage temperature; or

• 6 month duration with storage at both the proposed maximum storage temperature and at least 10 degrees higher; and

• at least 3 months duration at elevated humidity if the container is potentially moisture permeable.

If the stability studies would not support a shelf life of 12 months, the application may be considered premature and returned to the sponsor for resubmission when complete.

The TGA will accept for evaluation stability data generated using storage conditions as outlined in the EU document *Note for guidance on stability testing of existing active substances and related*
finished product (CPMP/QWP/556/96). However, the shelf life which is assigned to the product on the basis of such data will be determined according to the general principles outlined in this chapter.

The formulation of the finished product must be the same as that proposed for registration in Australia. It may be acceptable to provide stability data from similar formulation(s) as supporting data, subject to full stability testing being commenced on at least the first two production batches of the new product (refer to Post registration requirements in this Chapter). However it may be useful to contact the OTC Medicines Evaluation Section for advice in this regard.

Note that:

- A requested shelf life will not normally be approved for the purposes of registration if there are no data on the actual formulation registered.

The maximum permitted shelf life is five years.

Stability testing should be carried out in the container/closure system in which the product will be marketed in Australia. It may, however, be acceptable to provide stability data on the same formulation packaged in different materials, depending on the nature of the materials involved. It may be useful to contact the OTC Medicines Evaluation Section for advice in this regard.

Stability data in different container/closure systems are particularly relevant when studies of the two types of pack are provided which clearly show the equivalence or superiority of the container/closure system intended for registration over the system used in the stability studies.

Stability information should be generated on a minimum of two batches. All manufacturing processes should have been carried out on these batches (e.g., filtration, packaging, and sterilisation).

However, production batches may not be available at the product development stage. Where this is the case, a requested shelf life may be approved provided data are supplied on at least two pilot batches, subject to full stability testing being commenced on at least the first two production batches (refer to Post registration requirements in this Chapter).

As far as practicable, pilot batches must reflect the manufacture of full production batches using the same type of manufacturing equipment and the same manufacturing method. Pilot batches must be of sufficient size, appropriate to the dosage form and formulation, to be able to adequately reflect the physical conditions encountered in the manufacture of production batches. The use of laboratory scale batches is generally inappropriate.

Where the product is registered in several strengths, stability data should be generated on two batches of each strength. If the different strengths are a direct scale, at least one batch of each of the highest and lowest strengths should be tested.

Conditions of storage likely to be encountered in Australia should be a consideration in designing the stability study. Storage conditions should be clearly defined, preferably in terms of the categories specified in the Therapeutic Goods Order No 69 (or as revised from time to time):

- Store below –18°C (Deep freeze)
- Store below –5°C (Freeze)
- Store below 8°C (Refrigerate)
- Store at 2°C to 8°C (Refrigerate. Do not freeze)
- Store below 25°C

• Store below 30°C

The use of uncontrolled temperature conditions in stability studies is undesirable. Terms such as ‘room temperature’ and ‘normal warehouse conditions’ are discouraged, as these allow the product to be exposed to a wide range of conditions and make shelf life assessment difficult.

If storage in a refrigerator is proposed without the caution ‘Do not freeze’, then stability, particularly physical stability (eg. no formation of a precipitate, no denaturation of a protein) at about –5°C, must be demonstrated.

Stability studies at elevated temperatures are useful in predicting longer term shelf life periods from short term data. These predictions should be verified by studies on production batches to shelf life (refer to Prediction of shelf life from accelerated stability data and Post registration requirements, in this Chapter).

The cycling effect of night and day temperatures can be useful where the active ingredient is present partly in suspension and partly in solution. This should be considered in the design of stability studies for these types of products, where appropriate.

Where products are to be registered in potentially moisture permeable material such as polyvinyl chloride (PVC) or some grades of polyethylene, or where the closure system allows moisture transfer, the stability of the product should be determined under conditions of high humidity at the recommended temperature (refer also to High humidity studies in this Chapter).

Loss of moisture by transpiration can be important for some products, such as water based creams in moisture permeable containers. The extent of loss can be assessed by accurate weighing of marked individual packs over time. If severe, it may also be apparent as an increase in the concentration of active and/or non-active components in the product.

Where a sponsor asserts that the container or closure system is moisture-impermeable, evidence to this effect can be provided by, for example, the technique described in the USP test for containers-permeation (water vapour transmission). (Refer also to Chapter 11, Changes to OTC medicines.)

The possibility of leaching of substances from containers or closure systems into the product should be considered for any product where this could occur and may be a hazard, for example:

• ophthalmics supplied in non-glass containers or with plastic or rubber stoppers; or
• plastic components of metered dose aerosols.

**Appropriate tests**

**General**

Where test methods are identical to those in the routine quality control specifications, this should be stated.

Alternative test methods may be used in stability studies but they should be fully described and validated. Dissolution procedures other than those in finished product specifications are discouraged.

If changes are made to the assay or other test method during a stability study, data should be generated comparing the two methods to validate the change. Changes to dissolution test methodology during stability studies are strongly discouraged.

Where the results for a test, which is included in the expiry specifications, are unlikely to change during storage (eg. identification of the active substance or uniformity of tablet mass) there is no need to include that test in the stability studies.
Assay of active ingredients

A list of tests used in the stability studies indicating the test method used in each case should be provided. Where a test method is included in a pharmacopoeial monograph relevant to the product, the pharmacopoeial reference (e.g., BP) should be given. Where a test method is not included in a pharmacopoeial monograph, a full copy of that method should be attached.

Details should be provided of all analytical methods used in the stability studies together with validation data including:

- accuracy and precision in the range of the concentrations to be measured;
- shape of the calibration curve over the same range (linearity is preferred); and
- specificity, i.e., freedom from interference by degradation products, other likely impurities and excipients.

1. Examining the shape of the concentration/response curve

The shape of the concentration/response curve should be examined across the range of the analytical procedure. It is usually examined either by serial dilution of a standard stock solution or by preparing synthetic mixtures of product components. It is common to use five concentrations in the range 50-150% of the nominal sample concentration.

2. Demonstrating accuracy

The accuracy of a procedure is often determined in a recovery study in which an excipient (or placebo) blend is ‘spiked’ with a known quantity of the active substance.

3. Demonstrating precision

The precision of a procedure is generally determined by performing repeat assays of the product (with all steps including sample weighing and extraction being repeated). Data obtained on different days by different analysts and different equipment may be useful.

4. Demonstrating specificity in respect of excipients and extraction solvents

Specificity in respect of excipients is generally demonstrated by performing the assay procedure on an excipient (placebo) blend. Similarly, it is sometimes useful to demonstrate that extraction solvents do not interfere with the analysis by performing the assay procedure in the absence of a sample (or placebo sample).

Where a chromatographic procedure is used, copies of relevant chromatograms should be provided.

5. Demonstrating specificity in respect of degradation products

Sponsors should demonstrate that the test method is sensitive to degradation of the active ingredient.

- When the identity of all usual degradants is well known, specificity may be demonstrated by analysing the known degradants and demonstrating that they do not interfere with the analysis. It may be appropriate to analyse known degradants as pure substances and also when admixed with a sample extract or reference solution.
- When the identity of the degradants is not clear or when the sponsor does not have access to authentic specimens of the degradants, forced degradation studies should be undertaken. Commonly used forcing degradation conditions include treatment with
  - an aqueous solution of a mineral acid;
  - an aqueous solution of sodium hydroxide;
  - an aqueous solution of a strong oxidising solution such as hydrogen peroxide;
– heating the product;
– exposing the product to direct sunlight (or another source of ultraviolet light) for a prolonged period.

Some sponsors also choose to examine whether excipient degradants may interfere with the analysis by subjecting placebo blends to the forcing conditions.

Forced degradation studies are used to validate the test method (and not the finished product). In order to demonstrate that the test method is sensitive to degradation, it is necessary to demonstrate that degradation has occurred.

– Tabulated recovery data for the different degradation conditions and for non-degraded product are very useful for demonstrating that significant degradation has occurred for at least one of the degradation conditions.
– If degradation has not occurred under the conditions used, sponsors should consider using more forcing degradation conditions.
– Where a product contains more than one active, sponsors should consider whether degradants from one active can interfere with assay of the other active.
– Where degradation of the relevant active ingredient is intrinsically difficult to achieve, sponsors should justify not submitting the usual data.

Where a chromatographic procedure is used, copies of chromatograms relevant to the validation studies should be provided (including reference chromatograms, sample chromatograms, placebo chromatograms, and chromatograms of known degradants and/or chromatograms obtained in forced degradation studies).

Test methods must be validated and should be stability-indicating. Sponsors should note that pharmacopoeial methods are not necessarily stability-indicating.

Applications will not be accepted for evaluation where:

• the analytical methods used in stability studies are not stated; or
• the results of validation testing are not given or where the issue of validation is not addressed.

Useful information concerning validation of analytical procedures can be found in the EU notes for guidance on Validation of analytical methods: Definitions and terminology and Validation of analytical procedures: Methodology.

It is not sufficient to determine that the active content remains within the limits of the specifications; the study design and assay parameters should be such as to allow any trends over time to be observed.

It should be noted that loss of an active substance may be due to factors other than degradation, such as adsorption on to or absorption into the container wall, volatilisation, etc.

**Assay of preservatives**

As well as assay of active, it is usually necessary to assay any antimicrobial and antioxidant preservatives during stability testing. Stability-indicating validated assay methods should be used. (Refer also to Chapter 4D, Finished product specifications.)

**Degradation products**

Determination of trends in formation of major degradation products of the active substance may provide a better basis for determining a shelf life for a product than assay results for the active substance alone and should be considered where safety may be an issue.

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**Physical properties**

In addition to assay for content of active ingredient(s), it is also necessary to monitor the physical properties of the product during storage.

The physical tests will vary with the formulation in question but important attributes of the major dosage forms may include the following:

<table>
<thead>
<tr>
<th>Dosage form</th>
<th>Physical tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tablets and capsules</td>
<td>Dissolution or disintegration if dissolution is not relevant, appearance, odour, hardness, friability, moisture content, brittleness (hard gelatin capsules)</td>
</tr>
<tr>
<td>Liquid formulations</td>
<td>Appearance, colour, odour, pH, clarity (solutions) and particle size distributions (suspensions), resuspendibility (suspensions), viscosity, moisture content (powders for reconstitution), phase separation (emulsions)</td>
</tr>
<tr>
<td>Ointments and creams</td>
<td>Appearance, odour, viscosity, softening range, loss of water, physical and chemical homogeneity, particle size distribution, particle formation, pH, phase separation (emulsions)</td>
</tr>
<tr>
<td>Aerosols</td>
<td>Leak test, particulate contamination, valve function and appearance, weight loss. For metered dose aerosols refer to the BP monograph <em>Preparations for Inhalation of the British Pharmacopoeia</em> and also to the specific product monographs. Metered dose aerosols and some pump actuated aerosols will also require measurements of active ingredient mass aerodynamic particle size distribution on ageing</td>
</tr>
<tr>
<td>Suppositories and pessaries</td>
<td>Appearance, softening temperature (moulded products), dissolution rate (compressed products), disintegration testing</td>
</tr>
<tr>
<td>Freeze dried material</td>
<td>Appearance of both freeze dried and reconstituted material, pH, water content, rate of solution</td>
</tr>
<tr>
<td>(including materials for reconstitution)</td>
<td></td>
</tr>
<tr>
<td>Medicated soap bars</td>
<td>Appearance, odour, weight loss and pH</td>
</tr>
</tbody>
</table>

For other dosage forms not included in the above table, the sponsor should define the appropriate tests.

**In-use data**

'In-use' stability data should be generated where experience has shown that deterioration occurs once the container is opened, for example, with antacids and sterile preparations, such as those intended for ophthalmic use (refer also to Chapter 4D, *Finished product specifications*, and ‘Eye preparations’ in Chapter 9, *MEC guidelines*).

For sterile products that are intended for multiple use the preservative efficacy over the open shelf life period (eg. 4 weeks for eye preparations) must also be demonstrated (refer to *Preservative efficacy*).
The stability of the in-use form of the product should be established for the period of time and under the conditions for which storage is recommended.

Published papers may be submitted as evidence of in-use stability, provided they can be shown to be relevant to the formulation for registration and they include sufficient detail to allow independent evaluation.

See also Microbial content testing and Preservative efficacy.

Microbial content testing

All non-sterile dosage forms should include limits for microbial content in the expiry specifications unless departure from this requirement is justified (see Microbiological requirements – Non-sterile products in Chapter 4D). Where this exemption does not apply, microbial content testing should be carried out at the end (and preferably at the beginning) of shelf life during stability studies to demonstrate that the product remains within product specifications until expiry.

Preservative efficacy

Products that are intended for multi-dose use should be adequately preserved for the duration of the claimed shelf life. This applies to both non-sterile products (e.g. aqueous creams, lotions, and oral liquids) and sterile products (e.g. eye preparations). It is necessary to prevent microbial proliferation in, or microbial contamination of, such products during their normal conditions of storage and use.

During product development, preservative efficacy testing should be performed at the beginning and end of the claimed shelf life to demonstrate that the antimicrobial activity of the product as such or, if necessary, with the addition of a preservative(s), has not been impaired by storage. Data must be specific to the formulation and the container. If the requested shelf life is based on data generated under accelerated conditions, preservative efficacy tests should be performed on samples that have been stored at the higher temperature.

For all multi-dose products, tests in accordance with the BP/Ph. Eur. Efficacy of antimicrobial preservatives in pharmaceutical products are mandatory (consistent with Therapeutic Goods Committee resolutions 15/9, 16/10 and 16/11). Chemical assays of the level of preservative are not accepted as substitutes for biological tests.

For sterile products (e.g. eye preparations), that are intended for multiple use, the preservative efficacy of the product over the open shelf-life period (e.g. 4 weeks for eye preparations) must also be demonstrated. Such testing should involve repeated microbial challenges over the open shelf-life period as this most closely mimics the in-use situation. Alternatively, microbial content testing may be carried out on partially used containers that have been used by patients for the full open shelf life.

Modifications of a pharmacopeial preservative efficacy test (preferably the Ph. Eur./BP test) that include a rechallenge with reduced numbers of organisms could be used. Guidance may also be obtained from the normative part of the international standard ISO 14730 Ophthalmic optics – Contact lens care products – Antimicrobial preservative efficacy testing and guidance on determining discard dating which describes a test procedure and performance criteria for preservative efficacy over an open shelf life period of 28 days6.

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6 Note: This reference is not being supplied as a standard that must be applied to a product. It is supplied solely to demonstrate the elements of the type of tests that would be required to support an open shelf life period.
Dissolution rate

The behaviour of the dissolution rate over time should be examined as per the requirement in the relevant Therapeutic Goods Order or BP monograph. Dissolution profiles, generated by sampling at more than one time, may provide useful additional information about possible changes to the dissolution characteristics of the formulation during storage. Testing using a USP monograph method or in-house test method could be considered in the absence of a dissolution test in a relevant Therapeutic Goods Order or BP monograph.

High humidity studies

Data should be generated to establish the effect of high humidity on solid dosage forms packaged in container/closure systems which are likely to be moisture permeable. This includes containers made from polyvinyl chloride (PVC), with or without a PVDC coating, or low density polyethylene (LDPE); but does not include bottles made from glass or high density polyethylene (HDPE).

Satisfactory stability results when the product is stored at 25°C and 80% RH or 30°C and 75% RH for 3 months are normally sufficient to establish the adequacy of the packaging to protect the product from moisture for a period of up to 2 years. Data which show stability for a period of 6 months are normally sufficient to support a shelf life in excess of 2 years.

Stability data generated using samples stored at 40°C and 75% RH may also be useful (particularly in the absence of data generated at 25°C/80% RH or 30°C/75% RH). However, sponsors should note that, where rapid change in key stability parameters is observed for this storage condition, interpretation of the results may be difficult. In such cases (and also where the results do not comply with the expiry specifications), stability data generated with storage at 25°C/80% RH or 30°C/75% RH would be required.

Presentation of results

Results obtained at the commencement and at nominated time intervals throughout the study should be provided. This will allow any trends to be detected and will enhance the predictive value of the study.

Data which do not include initial results (i.e., at the start of the study) are of limited value.

Where possible, quantitative results should be quoted rather than a statement that the product complies with a particular specification. Assay results obtained during the study should be recorded either as absolute values (such as number of mg of active substance per capsule) or as a percentage of the nominal (labelled) content. If more than one assay result is available, expression of results as a percentage of the values at time zero is useful, but such figures are not sufficient by themselves.

For tablets and capsules, an average content should be obtained by conducting the assay on pooled samples, or by averaging individual dose unit results. This will minimise the effect of individual dose unit variations.

The results obtained should be discussed and explanations given where necessary, e.g., anomalous or unusual results, change in assay method, change in appearance.

Prediction of shelf life from accelerated stability data

The stability of a medicinal substance is directly related to the kinetics of the various degradation reactions. However, the relevant physicochemical equations are strictly applicable only when a single reaction occurs by a single mechanism. Because pharmaceutical products are usually mixtures of substances and may be in the solid state (for example, powders and tablets), these theoretical models do not necessarily hold and cannot be relied upon as predictive tools. The issue of physical stability (for example, dissolution rate and particle formation) adds a further
complication. There is, therefore, no substitute for the shelf life being determined empirically, ultimately over the shelf life.

However, it is acknowledged that the accumulation of stability data is a lengthy procedure and it is sometimes necessary to predict an interim shelf life for a product stored at a defined temperature from stability data obtained at an elevated temperature. This ‘accelerated’ stability testing is useful in providing information from which to assess the stability of a new product but it should be ultimately confirmed with long term stability studies at the recommended storage temperature for the duration of the nominated shelf life.

In most circumstances, the following general rule-of-thumb is used:

- If no trends are noted after storage for a period of (x) months at an elevated temperature (at least 10°C above the maximum storage temperature proposed for the product) then an interim shelf life of a maximum of 2(x) months may be permitted, where 2(x) does not exceed 3 years. For some products alternative interpretations may be considered, if justified.

Shelf lives of longer than 3 years should be supported by data on production batches stored at the maximum recommended temperature for the duration of the proposed shelf life. Stability studies involving at least two production batches, stored at the maximum recommended temperature, should be continued for the full period to validate the predicted shelf life (refer to Post registration requirements below).

**Post registration requirements**

Sponsors of therapeutic goods are required to carry out an ongoing stability testing program on each product (refer to clauses 1.2 and 6.2 of the Australian Code of Good Manufacturing Practice for medicinal products7. For more specific detail, contact the Manufacturer Assessment Section of the TGA).

Where a shelf life has been allocated on the basis of:

- accelerated testing; or
- data generated on a related formulation; or
- data generated on the same formulation in a different container; or
- data generated on batches other than production batches,

it is a requirement to provide an assurance that full stability testing will commence on at least the first two production batches and continue for the full period of the product's shelf life (at the recommended storage condition) and that any adverse trends will be reported to the TGA.

Data may be requested for review at any time or followed up by the TGA's auditors during GMP audits of the manufacturer. If it is found that the required testing has not been carried out or that adverse trends have not been reported to the TGA, appropriate action may be taken which may include cancellation of the product's registration.

**Requirements for a proposed stability testing protocol for self assessable shelf life extension**

A product’s shelf life may be extended on the basis of stability testing conducted according to a protocol which was specifically approved for this purpose. For a stability protocol to be considered for the purpose of self assessable shelf life extensions, it is normally necessary for at least 12

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months data, generated at the maximum recommended storage temperature, to be available on at least two production batches of the proposed formulation, in the container proposed for marketing, or one which is less protective.

To provide a suitable margin of safety, the limits for results of critical test parameters should normally be a little tighter than the expiry limits. Where some results are outside these limits, the sponsor may submit the data for evaluation by the TGA.

The protocol should be a standalone document which includes:

• a statement of the intended purpose (eg. "This protocol is intended for notification of shelf life increases of up to x years following self assessment of stability data");

• a statement of the criteria for notifying a shelf life increase (eg. "full term stability data will be generated using two production batches stored at y°C, all analytical results obtained will comply with the protocol acceptance criteria");

• the precise formulation of the product (if overages are included, this should be stated and a justification provided);

• the immediate container specifications;

• the storage conditions to be included on the label;

• the finished product expiry specifications and the protocol acceptance criteria (including acceptable limits for results of each test);

• a statement of the proposed tests and validated test methods (validation data should be included) (refer to Appropriate tests and Prediction of shelf life from accelerated stability data in this chapter); and

• a matrix indicating the time stations at which each of the tests will be conducted as well as the storage conditions to be used in the study.

**Shelf life extensions according to an approved protocol**

Provided that a protocol for self assessable shelf life extensions has been approved by the TGA for a particular product, the shelf life extension for that product may be implemented following notification to TGA (refer also to Chapter 11, Changes to OTC medicines), provided that:

all results up to the end of the notified shelf life fall within the acceptance criteria as specified in the approved stability protocol;

no other changes to the information about this product previously provided to TGA (other than specified in the notification) have been made, or are currently proposed to be made;

a stability testing protocol has been approved for the product and a copy of the approval letter is attached to the notification;

at least two full production batches of the Australian formulation product packed in the approved container have been used in the studies; and

the shelf life is not longer than the time for which stability data meeting the approved protocol are available, and in any case, is not longer than 5 years.
Prospective extensions of shelf life for individual batches

Under certain circumstances, the TGA may approve a limited extension of shelf life for individual batches approaching their expiry date in the absence of the stability data. The prerequisites are as follows:

- the existing shelf life should be at least 2 years;
- stability data are available to the TGA which validate the existing shelf life;
- a recent (less than 2 months old), dated certificate of analysis should be supplied for the batch, showing compliance with specifications, together with the results obtained at batch release; and
- the sponsor should provide an assurance that it has commenced or intends to commence a stability study to validate a permanent extension of the shelf life, unless it is purely intended as a one off required to ensure continued supply.

Prospective extensions of more than 6 months, or to a shelf life of more than 5 years, are not normally acceptable.

Checklist for submission of stability data

Evaluation time will be minimised where the design and reporting of stability studies follows these guidelines. It is in sponsors’ interest to follow these guidelines.

Use of the following checklist early in product development will reduce delays and requests for further information during the evaluation.

Ensure that you:

- specify the formulations used in the study and state which batches are identical to those proposed for registration in Australia;
- state whether the batches used in the study were laboratory, pilot or production batches;
- specify the size of each batch (e.g. 50 kg)
- clearly describe the packaging used in the study and confirm whether it is identical to the pack which will be used in Australia;
- present stability data on at least two batches of the product;
- specify the temperature, lighting and humidity conditions applied during the study;
- fully describe all test methods and sample sizes;
- provide validation of analytical methods (and include copies of relevant chromatograms);
- provide quantitative results where possible (in preference to “passes test” or similar wording);
- where possible, include quantitative or semi-quantitative determinations of the content of degradation products
- do not use an HPLC assay procedure to detect impurities without validation for this purpose. HPLC assay procedures as used for determination of the active ingredient may be unsuitable for separation and detection of impurities if they use too short a run time. Such a procedure would be acceptable if validated for impurity detection (note, however, that long run times do not in themselves ensure good separation);
• comment or conduct additional tests where there is a lack of balance between the formation of degradation products and the loss of the active substance. For example, are the assay procedures sufficiently specific? Is the active ingredient volatile? Is it adsorbed onto the container wall?

• consider additional tests to investigate the significance of obvious alterations in the characteristics of the product (eg. a distinct change in the colour of the product may necessitate additional investigation for degradation products);

• include relevant information on the physical characteristics of the product during storage, such as dissolution characteristics, homogeneity, particle size etc;

• include stability studies under conditions of high humidity for products which are to be registered in moisture-permeable containers, and especially for those which are potentially labile to moisture;

• provide results from sufficient time stations to allow assessment of any trends in the parameters;

• provide results for individual dosage units where these are available (eg. dissolution profiles).
4F. Microbiological testing

Introduction

Non-sterile pharmaceuticals should not contain excessive quantities of microbes, and pharmacopoeias suggest suitable test methods and limits. The ‘limit tests’ do not require the product to be sterile but instead prescribe the nature and amount of contamination which is tolerable.

Policy and procedures

All non-sterile pharmaceutical dosage forms should have limits for microbial content in expiry specifications.

If a sponsor claims that a non-sterile product cannot or need not have limits for microbial content in its expiry specifications, the TGA may still test the product for microbial content.

It is not a requirement that every batch of a product be tested for microbial content at release. Instead, for each product, manufacturers should aim to develop confidence that manufacturing procedures do not permit contamination by excessive numbers of microbes or by pathogenic microbes. This is achieved by testing routine production batches to establish a product history. It would normally be expected that the first 5 or 10 batches of a new product are tested at release. If satisfactory, testing could then be reduced to once every 6 to 12 months or on selected batches (eg. every tenth batch).

If the product is one that cannot easily be tested for microbial content (eg. a metered dose inhaler), the final bulk product can be tested and must comply. The test methods and limits which apply in this case are the same as if the product were tested in its final form.

Active raw materials do not need to include microbial specifications when there are suitable limits on the finished product.

USP and BP/Ph. Eur. methods and limits

The USP has a subchapter entitled Microbial Limits Test. The relevant BP section, Tests for Microbial Contamination, essentially adopts the tests and limits of the Ph. Eur. with some addition and rearrangement. TGA’s requirements differ somewhat from those of the BP/Ph. Eur. and USP as summarised in Table 1 below.

<table>
<thead>
<tr>
<th>BP/Ph. Eur. &amp; USP</th>
<th>Oral Products</th>
<th>Topical Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test Methods</td>
<td>Acceptable</td>
<td>Acceptable but need to add a medium which will permit growth of all pseudomonads and incubate at a suitable temperature (30-32 C)</td>
</tr>
<tr>
<td>Limits</td>
<td>Unacceptable</td>
<td>Acceptable but need to add requirements for the absence of all pseudomonads</td>
</tr>
</tbody>
</table>

Table 1: TGA Assessment of BP/Ph. Eur. & USP Microbial Specifications
Methods and limits acceptable in Australia

Acceptable test methods are those of the BP/Ph. Eur. and USP except that, for topical products, there should be an additional non-selective medium and incubation temperature (30-32°C) suitable for the detection of all pseudomonads rather than just *Pseudomonas aeruginosa*. No pseudomonads should be present. Other methods are acceptable provided they have been validated.

Acceptable limits on microbial content for non-sterile products are described in Table 2 (Guidelines for assessing the results of microbiological tests on non-sterile OTC medicines). Note that there are different limits for products for topical and oral administration, both quantitatively and qualitatively. The guidelines are only a broad indication of the microbial limits which may be applied. The list does not include every combination of number and type of undesirable organism which may make a product unfit for its intended use.

Products containing material of natural origin

Oral products should normally comply with the limits in Category 2a of the TGA Guidelines (Table 2). A manufacturer may apply Category 2b limits if the product contains materials of natural origin.

The BP and the Ph. Eur. requirements for *Microbial Quality of Pharmaceutical Preparations* include a category for oral products containing materials of natural origin (plant, animal or mineral). Table 2 also includes a category for products for oral use containing raw materials of vegetable or animal origin. The BP/Ph. Eur. further defines these materials as those "for which antimicrobial pretreatment is not feasible and for which the competent authority accepts a microbial contamination of the raw material exceeding 10³ viable micro-organisms per gram or per millilitre."

The TGA does not require general microbial limits for raw materials. The only stipulation is that the finished products that contain these raw materials must comply with the TGA Guidelines.

The types of materials which would be classified as being 'of natural origin' and which would cause products containing them to be classified Category 3b (BP/Ph. Eur.) or 2b (Table 2) are raw plant materials or animal material which have not been fully processed.

Topical products

These products should normally comply with the limits in Category 1a of the TGA Guidelines (Table 2), or Category 1b if they contain antiseptics or corticosteroids.

Surgical scrubs and pre-operative preparations should comply with the limits in Category 1b.

Products for nasal or oral/pharyngeal use

*Guideline amended 25 June 2004*

Limits on the microbial content of products intended for use in the nasal or oral/pharyngeal cavities should be the same as those applied to topical products (Category 1a, or Category 1b if they contain antiseptics or corticosteroids, Table 2). They should also be free of *E. coli* in 1 g and *Salmonellae* in 10 g.

Transdermal patches

Limits on the microbial content of transdermal patches should be the same as those applied to topical products (Category 1a, Table 2), except that the limits apply per patch instead of per gram. The same requirements for absence of all pseudomonads also applies to transdermal patches.

Rectal Products

Limits on the microbial content of rectal products should be the same as those applied to oral products (Category 2a or 2b, Table 2).
Table 2: Guidelines for assessing the results of microbiological tests on non-sterile OTC medicines

<table>
<thead>
<tr>
<th>Category</th>
<th>Type of preparation</th>
<th>Suggested limit</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Products for topical application (including those for use in body cavities)</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| 1a | For use on broken* and unbroken skin (other than antiseptics and corticosteroids) | TAMC** not more than $10^2$ per mL or per g, amongst which there should be:  
no pseudomonads  
no *Staph aureus* |
| 1b | Antiseptics, corticosteroids | TAMC** not more than 10 per mL or per g, amongst which there should be:  
no pseudomonads  
no *Staph aureus* |
| **Products for oral use** | | |
| 2a | Products other than those containing raw materials of vegetable or animal origin | TAMC** not more than $10^3$ per mL or per g, amongst which there should be:  
not more than $10^2$ yeast and mould in 1 mL or 1 g  
not more than $10^5$ enterobacteria in 1 mL or 1 g, with  
no *E. coli* in 1 mL or 1 g  
no salmonellae in 10 mL or 10 g |
| 2b | Products containing raw materials of vegetable or animal origin | TAMC** not more than 104 per mL or per g, amongst which there should be:  
not more than $10^2$ yeast and mould in 1 mL or 1 g  
not more than $10^5$ enterobacteria in 1 mL or 1 g, with  
no *E. coli* in 1 mL or 1 g  
no salmonellae in 10 mL or 10 g |

* 'broken skin' refers to minor cuts and abrasions; products intended for use on large open wounds or severely damaged skin should be sterile.  
** Total aerobic microbial count
5. Presentation

Introduction

The presentation of OTC medicines is critical for their safe use. It is defined in the Therapeutic Goods Act 1989 (Section 3) as “the way in which the goods are presented for supply, including matters relating to the name of the goods, the labelling and packaging of the goods and any advertising or other informational material associated with the goods”. Presentation is one of the factors that must be taken into account by the TGA delegate in making decisions on the registration of medicines (Section 25).

The Act states that the presentation of a medicine is unacceptable:

- if it is capable of being misleading or confusing as to the content or proper use of the goods
- if it states or suggests that the goods have ingredients, components or characteristics that they do not have;
- if a name applied to the goods is the same as the name applied to other therapeutic goods that are supplied in Australia where those other goods contain additional or different therapeutically active ingredients; or
- if the label of the goods does not declare the presence of a therapeutically active ingredient; or
- if a form of presentation of the goods may lead to unsafe use of the goods or suggests a purpose that is not in accordance with conditions applicable to the supply of the goods in Australia.

This Chapter describes various aspects of presentation and gives guidance on what constitutes acceptable presentation for OTC medicines. It is divided into five sections as follows:

5A Product name
5B Labelling
5C Product Information
5D Consumer Medicine Information
5E Changes to scheduling
5A. Product name

Interpretation of ‘name’

This section provides an interpretation of the meaning of ‘name’ as used in Section 16 of the Therapeutic Goods Act 1989 and as applied to medicines. Under s.16, goods are regarded as ‘separate and distinct’ if they differ from other goods in any of the following features:

a) formulation, composition or design specification;

b) strength or size (disregarding pack size);

c) dosage form or model;

d) name;

e) indications;

f) directions for use;

g) different type of container (disregarding container size).

For the purposes of determining whether medicines which are the same in characteristics (a)-(c) and (e)-(g), have a different name, the information which appears on the label(s) attached to the goods (eg. printed on the package or container) when the goods are supplied is considered. The ‘name’ is regarded as including one or more of the following (terms used are as defined in the Labelling Order1):

- a specific registered trade mark name given to the product (‘proprietary name’);

- a unique word or code given to the product (‘proprietary name’);

- a description of unique characteristics of the product (‘non-proprietary name’);

- a registered trade mark or other unique name, mark or logo belonging to the manufacturer or supplier (eg. company trading name, which appears prominently on the label other than as an integral part of the information giving name and address of the sponsor, manufacturer or distributor;

- a registered trade mark or other unique name, mark or logo belonging to the manufacturer or supplier (eg. company trading name), which appears as an integral part of the name and address of the sponsor, manufacturer or distributor, in a prominent location on the main label in letters of equal or greater size than is used for the name of the active substances in the goods;

- a distinctive colour or label presentation/layout.

‘Umbrella’ / family brand names

Added 13 February 2004

This guideline has been adopted by the TGA on an interim basis pending the development of guidelines for the Australia – New Zealand Joint Agency. The guideline does not introduce any new policy but is a clarification of existing policy in relation to unacceptable presentation of umbrella branded products².

‘Umbrella’ or ‘family’ branding describes the situation where a sponsor markets different products under the one brand name (eg. Strepsils lozenges, Strepsils mouthwash, Strepsils Family Cough Medicine).

The use of a well-known brand name on new products with different active ingredients for either the same or a different indication could cause the consumer or health care practitioner to confuse the current products and the new product. In these circumstances, the ‘presentation’ of the product may be ‘unacceptable’ (see Page 5.1 of this Chapter for a discussion of ‘unacceptable presentation’).

Where the brand name is strongly associated with a particular active and there are significant differences in the safety, efficacy or dose regimen of the current and proposed products, the new product will not be accepted under the proposed trade name.

In cases where the brand name is not strongly associated with a particular active or combination of actives and there are no significant differences in the safety, efficacy or dose regimen of the current and proposed products, the potential for confusion may be able to be addressed by clear differentiation of the packaging and labelling of the new product to the extent that it will be immediately apparent to consumers that they are dealing with a different product. In some cases this may require modification of the labels of the new product and all products in the existing range to include the name of the active ingredient as part of the product name using the same font style and size.

In assessing whether the use of an existing brand name for a new product with different active ingredients is acceptable, the following points are considered:

a) Association

The strength of association of the brand name with a particular active substance and/or therapeutic use:

• history of marketing and advertising;
• the extent of prescribing by medical practitioners and recommendation by pharmacists (including whether the brand is or has been listed on the PBS);
• the number and proportion of products within the brand range with a particular active substance;
• the presence of products within the brand range that have a different active substance(s).

² Statement added for clarification – 30 July 2004
b) Differentiation

Whether the presentation of the new product is sufficiently different to the existing product range to alert consumers to the fact that this is a different product, despite the similarity in product name:

- Wording (particularly the prominence of identification of the active ingredient) on the labels of proposed product and existing product(s);
- Pack colour, shape, size, layout and design;
- The dosage form – visual appearance, physical characteristics, smell and taste;
- The likelihood that consumers will mistake the new product for the existing one at the point of sale and at the point of use (eg. at a child’s bedside in the middle of the night).

c) Safety

Consider the consequences if a consumer took the new product as if it were the existing product and vice-versa.

Consider sub-groups for which there may be specific safety concerns, eg. consumers with gastric ulcer or asthma if the products are confused

Consider the conditions the new product and existing products are intended to treat. If the conditions are different (eg. the existing products are all antifungal and the new product is an antiviral), are there any safety concerns if a consumer confuses the products?

d) Efficacy

Consider the consequences if a consumer took the new product as if it were the existing product and vice-versa.

If the dose is different (amount, frequency or duration) or if the conditions to be treated by the existing and new products are different, are there any efficacy concerns if the consumer confuses the new and existing products?

e) Other information

- The classification of the product – is professional advice available / required at the point of sale?
- The sponsor’s proposals for advertising / consumer education / practitioner education.
- Evidence of consumer testing to demonstrate adequate differentiation between the products.

The decision:

The decision is made by a delegate of the Secretary following a balanced consideration of all relevant factors. The primary consideration here is "whether the presentation of the goods is acceptable" (s25(1)(e), Therapeutic Goods Act 1989).

‘Own name’ products

‘Own name’ products are those that are identified on the label as being associated with a particular retailer or marketing group.

‘Own name’ OTC products can be supplied under two alternative arrangements:

a) Separate registration/listing

Where a sponsor or retailer wants to label a product with a name that is unique to a particular retailer (eg. ‘Carter’s Cold Tablets’) a separate entry is required in the ARTG and the product will carry an AUST R/L number unique to that product.
b) Use of an existing registered/listed product

Under this arrangement some retailer identification may be included on the label of an existing registered/listed OTC product without requiring a separate entry in the ARTG. The product will continue to be registered in the ARTG by the original sponsor and carry the product's AUST R number.

In these instances, the product can be labelled with either or both of the following:

- **On the main label,** identifying details of the retailer in a font size not larger than that used for the active ingredients preceded by the words “sold by” or “made for” or “manufactured for” or “distributed by”;

- **On another part of the product** (eg. on the back label), identifying details of the retailer in a font size not larger than that used for the product name preceded by the words “sold by” or “made for” or “manufactured for” or “distributed by”.

### Professional endorsement

Pharmacists, pharmacy marketing groups, hospitals or other health professionals may wish to register or list products under their own name (eg. 'Carter's Cold tablets' as above). Care needs to be taken to ensure that the name of the product, and any other information on the label, does not breach the ‘professional endorsement’ provisions of the [Therapeutic Goods Advertising Code](http://www.tgacc.com.au/) (a label is an ‘advertisement’ as defined in Section 3 of the [Therapeutic Goods Act 1989](http://www.tga.gov.au/industry/scheduling-poisons-standard.htm)).

The Code requires that advertisements must not contain or imply endorsement by 'individual healthcare professionals', other than where the emphasis is on ‘availability’ or by 'hospitals and other facilities providing healthcare services'.

Certain medicines are usually only available through pharmacies (those included in Schedules 2 and 3 of the [Standard for the uniform scheduling of drugs and poisons](http://www.tga.gov.au/industry/scheduling-poisons-standard.htm)). These medicines must include the signal heading “Pharmacy Medicine” or “Pharmacist Only Medicine”. These signal headings do not breach the Code because they describe the availability of the product – ie. you must visit a pharmacy to purchase products in either category but must consult the pharmacist to purchase a ‘Pharmacist Only Medicine’ product.

Where names of products are proposed that include references to pharmacy or pharmacists or other healthcare professionals, it needs to be considered whether the reference is to ‘availability’ or whether it constitutes ‘endorsement’ by the pharmacist or by the ‘facility providing healthcare services’ (eg. the pharmacy).

For instance, the words “Pharmacy formula” or “Pharmacy Only” would not be taken to breach the Code because they are a reference to ‘availability’. This interpretation only applies where a product is sold exclusively in pharmacies. If, for example, a paracetamol product bearing the name “Pharmacy formula” were to be sold in a supermarket, the reference to “pharmacy” could be interpreted as an endorsement by the pharmacy profession and would therefore be in breach of the Code.

- **Where a pharmacy marketing group has a name that clearly implies professional recommendation** (eg. “Pharmacist Advice”), the name and/or logo of the marketing group can only appear on product labels where it can be established that this name/logo is strongly linked with the point of supply. This could be the case in the following circumstances:

- **Pharmacies subscribing to the marketing group are required to be identified with the name of the marketing group; and**
• The products are not available to retail outlets that are not members of the marketing group; and

• The name/logo of the marketing group appears on the label in close proximity to the product's name; or

• The name/logo of the marketing group appears elsewhere on the label and is a registered trade mark of the marketing group.

Where the above does not apply and the sponsor's name implies professional recommendation, that name cannot be used as part of the product name but can be included in small font, not on the main label, as part of the sponsor's name and address as required by TGO 48/69, without breaching the Code.

Products that have names that breach the professional recommendation provisions of the Therapeutic Goods Advertising Code\(^5\) will not be approved.

Names that have been accepted to date include 'Chemists' Own', 'XX Chemists', 'Health Care Chemist', 'XXX Pharmacy', 'Pharmacist', 'Pharmacist Formula', 'Pharmacy Formula', 'Pharmacy Health' and 'Pharmacist Advice'.

5B. Labelling

This section describes the requirements for labels and package inserts. A product’s label (as defined in the *Therapeutic Goods Act 1989*) includes the label attached to the container (eg. bottle, tube or blister pack), the primary pack (eg. carton) and any printed information supplied with the container or primary pack (eg. package insert).

Copies of all draft product labels (including package inserts) should be provided with applications to register new products or vary the labelling of current products. Where the only difference in labelling between pack sizes is the pack size, only one set of labels need be provided if an assurance to that effect is provided with the application.

Full colour drafts should be provided during the evaluation process or prior to approval, to allow a thorough assessment of the product’s presentation. Colour photocopies are preferred but electronic copies will be accepted if these are not available.

Labels should comply with the following documents:

- the Standard for the uniform scheduling of drugs and poisons (SUSDP)\(^1\);
- the Labelling Order\(^2\);
- Chapter 9 – [MEC guidelines];
- the Therapeutic Goods Regulations; and
- the Therapeutic Goods Advertising Code\(^3\).

The new product application form (*New medicine registration application form (OTC – Over the counter medicines)*\(^4\)) includes a label checklist that will assist in ensuring that labels comply with these requirements. Sponsors should also take care to ensure that label text is expressed clearly, accurately and concisely. This may save considerable time during the evaluation phase.

Changes to the labels or package inserts of existing products usually require approval or notification to the TGA. Details can be found in Chapter 11, [Changes to OTC medicines](http://www.tga.gov.au/industry/scheduling-poisons-standard.htm).

Other Commonwealth and State/Territory legislation may need to be taken into account when labelling medicines, eg. *Trade Practices Act 1974*, Division 1A – Country of origin representations, *Commerce (Trade Descriptions) Act 1905* and *Commerce Imports Regulations 1940\(^5\)*, Tamper-Evident Packaging (TEP) requirements\(^6\), Trade Measurement, Deceptive Packaging, Packaging Covenant\(^7\). Note that the above list is indicative only.

**Statement of ingredients**

The Labelling Order\(^8\) specifies how active ingredients should be declared on labels. The Order also requires the disclosure of specified excipients (eg. those that are known to cause adverse effects in

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some individuals; antimicrobial preservatives in products for topical use) and specifies how these are to be declared on labels.

Selective disclosure of excipients not required to be disclosed by the Labelling Order will need to be justified, eg. flavours, colours.

In addition, the selective disclosure of individual excipients, where this could imply that the excipient may have a therapeutic activity, will not be accepted, eg. menthol, vitamin C, vitamin E.

A product label may include a statement that the product does not contain an excipient known to cause adverse effects in some individuals (eg. gluten free, sugar free, alcohol free) provided the statement is true.

Inclusion of a statement that the product contains no sugar is acceptable provided that sucrose, glucose, fructose and other sugars with a cariogenic potential or the potential to affect people with diabetes are not included in the formulation. If the formulation includes any proprietary ingredients, the sponsor should check with the manufacturer of the proprietary ingredient that it does not contain the specified component.

Directions for use and dosage

Directions for use must clearly identify the dose and dosage frequency for each target population for which the product is intended (eg. “Adults and children over 12 years: two tablets twice daily; Children 6 to 12 years: one tablet twice daily”). If the product is not intended for use in children, the label should specify that the dose is an adult dose (eg. “Adult dose: 10 mL”). The maximum daily dose for each age group should be included where appropriate.

Where the labelling only includes doses for adults and/or children over a specified age (eg. Adults and children 12 years and over; children from 7 years), the label should include a statement such as “Do not give to children under xx years” or “Not recommended for children under xx years”.

Statements such as “Do not give to children under xx years except on medical advice” or “Not recommended for children under xx years except on medical advice” are acceptable only if the product has a TGA-approved published Product Information (PI) that the doctor can refer to in determining the appropriate dose for this age group.

The directions for products which are intended for symptomatic relief (eg. cough and cold preparations) should include a qualifier such as ‘as required’ or ‘when necessary’ after the specific dosage frequency (eg. “twice daily when necessary”). The directions “as required” or “when necessary” are not acceptable on their own.

Labelling should recommend use of metric measuring devices to accurately measure doses. If the recommended doses cannot be measured using a readily available metric measuring device, a suitable measuring device should be provided in the pack.

For solid or semi-solid dose forms such as powders or gels, if the labelled dose corresponds to the quantity contained in one or more level 5 mL medicinal measuring spoons, a dosage stated in that way would be acceptable (eg. “Adult dose: one level 5 mL medicinal measuring spoonful…”).

References to culinary ‘spoonsful’ (eg. teaspoon, dessertspoon, tablespoon, etc) will not be accepted.

Warning statements and contraindications

Warning statements required by the SUSDP must be stated on the product label. Statements specified in Chapter 9, MEC guidelines, should be included on the label and/or package insert, as appropriate.
Distinctiveness of labels

To reduce the possibility of confusion among consumers, the presentation of new products (including pack design, font size and type, logos, etc) should be such that the new products are clearly distinguishable from existing products.

Graphics, logos and symbols

Non-corporate graphics, logos or symbols on labels should be appropriate for the claimed therapeutic use of the product. For example,

- an illustration of a baby would be inappropriate for a product with a dose range starting at 2 years and
- a graphic highlighting joints would be inappropriate for a product that is indicated for use only on soft tissue injuries.

Pregnancy warning statement

Where the product contains active ingredient(s) that are included in any category other than category 'A' in the ADEC publication *Prescribing medicines in pregnancy*[^9], the label should include a statement advising consumers who are pregnant or who may become pregnant to check with their doctor or pharmacist before taking or using the medicine.

Use of the term ‘easy breathing’

Terms that imply ‘easy breathing’ may mislead people with asthma. Such terms will not be accepted in isolation, but must be qualified by reference to the actual condition being treated (e.g. "by drying the secretions of the nose, this product makes breathing easier").

Reference to other products

There are several situations where other products may be referred to in labelling. These include:

- reference to more suitable dosage forms within the same range for different age groups (see Family packs guideline in Chapter 9, *MEC guidelines*);
- reference to another product that can be used in conjunction with the current product;
- reference in labelling to a sponsor's other products within the same product range that have the same trade name as the current product.

The products referred to must be approved for supply in Australia.

It is important that references to other products should not be capable of confusing the consumer (e.g. the statement "from the makers of Xxx" on the front panel of a label may lead some consumers to think the product is 'Xxx').

Comparison

Statements comparing a product with other products or treatments will only be accepted where satisfactory evidence is provided to support the claim. Refer to the Therapeutic Goods Advertising Code\(^\text{10}\) (Clause 4.3).

Endorsements

Labels must not contain or imply endorsement of the product except as permitted by the Therapeutic Goods Advertising Code\(^\text{11}\) (Clause 4.4).

The sponsor should remove an endorsement from the labelling (by way of a notification application to the TGA) once the endorsement is no longer applicable.

Internet addresses

The inclusion of Internet addresses on labelling is only acceptable if the sponsor provides an assurance that the information about the product included on the website (including any direct links from that website) is consistent with the information approved by the TGA for that product. If such an assurance cannot be provided, the Internet address should be deleted from the labelling.

Foreign language text on labels

Products that are supplied in Australia and also exported may have a dual label (one for Australia and one for the importing country). These labels can include overseas product registration numbers or other information that is required by the importing country.

A certified English translation of any other language must be provided to verify that the text is consistent with the English language text and that the label, including the product name, does not include or imply any additional indications.

\(^{10}\)\(\text{http://www.tgacc.com.au/}\)

\(^{11}\)\(\text{http://www.tgacc.com.au/}\)
5C. Product Information (PI)

Amended 16 May 2011

Introduction

The product information document contains technical information about the medicine such as the characteristics of the active ingredient, its indications and contraindications, a description of clinical trials relevant to the indications, precautions, adverse reactions that may occur from the use of the medicine, dosages and storage, and other information relating to the safe and effective use of the medicine.

The purpose of a product information document is to assist medical practitioners, pharmacists and other health professionals in prescribing and dispensing the medicine, and to assist them to provide patient education about the medicine to support high quality and safe clinical care. The product information document is to present a scientific, objective account of the medicine's usefulness and limitations as shown by the data supporting the application. It is to be devoid of promotional material.

Form

As a part of an application to register a 'restricted medicine', a draft product information document must be lodged in a form approved by the Secretary under section 7D of the Therapeutic Goods Act 1989 (the Act). This is the Form for providing product information for a restricted medicine or other medicine in relation to which the secretary requires product information to be provided.1

Restricted medicines are defined in the Restricted Medicine Specification 20112 and include prescription medicines (see Schedules 4 and 8 of the current Poisons Standard) and medicines only available from a pharmacist (Schedule 3 of the current Poisons Standard3). The Secretary can also require other higher risk medicines to have approved product information where appropriate.

Examples of OTC medicines that are not 'Pharmacist Only Medicine' (Schedule 3) products which may require a PI include:

- Products with active ingredients that are new chemical entities (NCEs);
- Products often prescribed by medical practitioners (eg. sucralfate, glyceryl trinitrate); and
- Products that are not adequately documented in standard reference texts (eg. Martindale).

The form for the product information and the Restricted Medicine Specification 20114 can be found on the TGA web site.

All applications to register 'Pharmacist Only Medicines' (Schedule 3) must be accompanied by a draft PI document which will be evaluated as part of the application. For those products that have moved from 'Prescription Only Medicine' (Schedule 4) status, where no changes have been made to the TGA-approved PI, a copy of the approved PI should be included in the application.

Applications to vary an entry on the ARTG or change the conditions to which the inclusion of the medicine is subject, and require a change to the existing product information must include a draft product information document in the application.

After registration, the product information cannot now be changed without TGA approval.
5D. Consumer Medicine Information (CMI)

The *Therapeutic Goods Regulations 1990* require that sponsors supply Consumer Medicine Information (CMI) with all ‘Pharmacist Only Medicine’ (Schedule 3) products approved for registration after 4 July 1995. All ‘Pharmacist Only Medicine’ (Schedule 3) products will require a CMI from 1 January 2004.

The CMI must be:

- written in English,
- clearly legible,
- written in language that can easily be understood by patients, and
- consistent with the PI.

The CMI must comply with the requirements specified in Schedule 13 to the Regulations, although the information does not have to be set out as listed there. CMIs must not include promotional material (refer to the ASMI *Code of Practice* for further information regarding promotional material).

The sponsor is responsible for writing, updating, and distributing CMI to the point of supply of a medicine to the patient.

The CMI may be provided in the primary pack (eg. as a leaflet in the carton) or ‘in another manner’ (eg. in electronic form via pharmacy computers).

The short patient information leaflets generated as part of some pharmacy software dispensing programs are not CMI, as they do not contain the level of information required for consistency with the PI, and are not necessarily updated when PI updates occur. A patient leaflet or disease management leaflet is not a CMI.

Sponsors are strongly encouraged to refer to the publication *Writing about medicines for people – Usability guidelines for consumer medicine information*, and the Core CMIs* when writing CMIs.

* available from the Communication Research Institute of Australia.

** refer to the ASMI website for available Core CMIs.

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New products

A new ‘Pharmacist Only Medicine’ (Schedule 3) classification can come about as a result of various situations:

- Down-scheduling from ‘Prescription Only Medicine’ (Schedule 4) status – these products already have a PI. Where no changes to the current PI and CMI documents are proposed, the sponsor should provide a copy of the current PI and CMI, together with an assurance that no changes have been made to these documents. Changes to the PI and/or CMI may be needed if only some of the prescription indications are approved for the non-prescription product, and to ensure that the directions for use are consistent with those on the ‘Pharmacist Only Medicine’ (Schedule 3) product labelling. Other aspects of the PI and/or CMI may also need to be updated.

- Up-scheduling from unscheduled or ‘Pharmacy Medicine’ (Schedule 2) to ‘Pharmacist Only Medicine’ (Schedule 3) status – a PI and CMI will need to be written. Applications for registration must be accompanied by draft PI and CMI documents, which will be evaluated as part of the application.

- New chemical entity – a PI and CMI will need to be written. Applications for registration must be accompanied by draft PI and CMI documents, which will be evaluated as part of the application.

Existing products

CMI will also be required for ‘Pharmacist Only Medicine’ (Schedule 3) products registered prior to 4 July 1995 where a change to the product is such that it requires an additional, grouped, register entry (eg. change of name, change of flavouring agent). An explanation of ‘grouping’ is given in Chapter 11, Changes to OTC medicines).

As is the case with PIs, a draft CMI should be submitted for approval by 31 December 2003 for those ‘Pharmacist Only Medicine’ (Schedule 3) products which were approved for registration before 4 July 1995 (refer to Chapter SC, Product Information).

Changes to CMIs

Changes to CMIs that are not supplied as a package insert need not be approved by, or notified to, the TGA. Where a change is required as a result of an amendment to the PI, the CMI should be updated without delay to ensure that it is consistent with the PI, as required by Schedule 13 of the Therapeutic Goods Regulations.

Changes to CMIs that are supplied as a package insert are treated in the same way as changes to product labelling. The requirements for these changes are specified in Chapter 11, Changes to OTC medicines).
5E. Changes to scheduling

When the classification of a product is changed following a decision of the National Drugs and Poisons Schedule Committee (NDPSC), changes will be required to labels and possibly package inserts, PI and CMI.

The regulatory responsibility for dealing with changes to a product that is currently 'Prescription Only Medicine' (Schedule 4) rests with the TGA’s Drug Safety and Evaluation Branch. However, the Non-prescription Medicines Branch (NPMB) will consider applications for changes to these products when the NDPSC has made an initial decision to move the medicine to a non-prescription category. If the decision is not confirmed by the NDPSC, the application must be withdrawn.

The sponsor is responsible for ensuring that labelling and any other changes arising out of a rescheduling decision are either notified to or approved by the NPMB as specified in Chapter 11, Changes to OTC medicines.

Products containing a ‘Pharmacist Only Medicine’ (Schedule 3) substance require Product Information (PI) and Consumer Medicine Information (CMI). This is not the case for products containing ‘Pharmacy Only’ (Schedule 2) or unscheduled substances; however, a PI may be required for some products (refer to Chapter 5C, Product information).

Products must not be supplied under the new scheduling arrangements prior to the effective date as specified in the SUSDP.
6A. Efficacy and safety

The Therapeutic Goods Act 1989 requires that applications for registration be evaluated “having regard to whether the quality safety and efficacy of the goods for the purposes for which they are to be used have been satisfactorily established”.

This Chapter sets out the information that should be submitted to support the efficacy and safety of a registrable OTC medicine. Deviations from these guidelines may be accepted provided sound justification is given.

For full dossiers, sponsors are encouraged to submit according to the CTD (Common Technical Document) format or in the ‘old’ European Union (EU) format. Details of these guidelines can be found on the TGA website\(^1\).

Well documented active ingredients

Where adequate information on the use of each active ingredient in the formulation is contained in standard reference texts and/or these guidelines, further information on the safety and efficacy of the product is not required (e.g. paracetamol administered orally at a dose of 500 mg to 1 g every 4 to 6 hours for pain relief in adults). The majority of OTC medicines will fall into this category.

The following are examples of reference texts which are usually acceptable as sources of information on the safety, efficacy and dosage regimen of ingredients in an OTC medicine:

- Martindale: The complete drug reference, Sweetman SC (Ed.), Pharmaceutical Press, UK
- Handbook of nonprescription drugs, American Pharmaceutical Association, USA
- Remington’s Pharmaceutical sciences, Gennaro AR (Ed.), Mack Publishing Company, USA
- Handbook of pharmaceutical excipients, Kibbe AH (Ed.), American Pharmaceutical Association, USA and Pharmaceutical Press, UK
- AHFS Drug information, McEvoy GK (Ed.), American Society of Health System Pharmacists, USA

Use outside of documented indication(s) and/or dosages, as well as new routes of administration will require evidence of efficacy and safety unless otherwise justified (refer ‘The submission’ section below). It should be noted that anecdotal, or limited clinical reports of efficacy alone (for example, in Martindale “xxxx has also been used in …”) are not regarded as adequate evidence of efficacy and safety.

Applications for products with well documented ingredients should include an overview or covering letter giving details of the relevant texts (photocopies of the relevant pages are preferred) with particular reference to the accepted indications and dosage of the active ingredient(s). Sponsors may choose to submit information on global regulatory status indicating those countries in which the proposed indication and dosage have been approved.

Products containing active ingredients that are not well documented

Where the use of any ingredient is not well documented in standard reference texts, further evidence of safety and efficacy will be required. Unpublished clinical studies with significant

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supporting data (not summary information) are acceptable as well as reports published in ‘peer reviewed’ journals. Sponsors should make sure that any studies that are provided are of a sound scientific standard.

Information on the process for approval of a ‘new’ active or excipient substance (ie. one which is not included in any products currently entered in the register for supply in Australia) is included in Chapter 6B, New substances.

If there is inadequate evidence of efficacy and/or safety in the published scientific literature for the active ingredients or the product or for the proposed indication or dosage, it will be necessary to provide reports of clinical trials that the sponsor has conducted to establish the efficacy and safety of the product proposed for registration. These trials should be performed and reported according to established ethical, scientific and clinical practice.

The submission

Whether the submission is bibliographic or in the form of specific trials conducted on the product proposed for registration, it should include:

- an index of contents;
- an overview referenced to the submission by page number;
- an expert report referenced to the submission by page number;
- full copies (not abstracts) of all relevant reports and clinical trials.

Bibliographic submissions

A bibliographic submission may be appropriate where adequate evidence of safety and efficacy is available in the published scientific literature.

A bibliographic submission should represent a comprehensive and unbiased review of the available literature in relation to the application using a medical/scientific database such as Medline. For older drugs or where relevant reports are few, the search may need to include all records in Medline and/or other databases such as Embase. Details of the search strategy should be included (preferably on disk as well as hard copy) to enable critical analysis by TGA librarians or duplication of the search if necessary.

Published reports of clinical trials should only be included in the submission where:

- the trials are conducted using the same active ingredient(s) with a similar dosage regimen, dose form and route of administration to the product proposed for registration;
- the trials are reported in sufficient detail to allow an independent assessment of the results (including methods and a statistical analysis of the results) in relation to the efficacy and safety of the product proposed for registration.

Trials should be excluded if they are conducted on different actives, for different indications or different routes of administration or are poorly conducted or reported or not of sufficient power to produce statistically significant results.

Well-conducted, published reviews may be of assistance as supporting material and should be included where relevant.

A list or table of reports which have been excluded from consideration should be presented together with reasons for the exclusion. All relevant, well-conducted and reported trials should be included regardless of whether their findings are adverse to the product proposed for registration.
Guidance on literature based submissions may be found on the TGA website\(^2\).

**The overview**

The overview should include a table with summary details of all reports which are present in the submission including:

- abbreviated publication details (author(s) and journal reference) where relevant;
- the type of report (eg. double blind, randomised, multi-centre, cross-over trial);
- the number of subjects included in the trial;
- the duration of the trial;
- a brief statement of conclusions in terms of efficacy and safety; and
- details of the dose form, formulation and dosage schedule of the product used in the trial.

The sponsor should indicate those studies that are considered pivotal to the submission, and their reasons for doing so. Data from randomised, double blind, controlled studies would be expected to be given greater weight than data from non-randomised, uncontrolled or open studies.

With regard to safety data, there should also be tabulation and appreciation of all adverse events (including abnormal laboratory values, drug interactions etc) for all documented clinical studies and any adverse events which have been reported to the sponsor.

All submitted data/papers etc should be cross-referenced to the submission to allow the papers to be located easily.

For bibliographic submissions, the overview should also include a list or table of reports, which have been excluded from consideration together with reasons for the exclusion.

The overview may be included as part of the expert report (see below) or as a separate document.

**The expert report**

Whether the submission is bibliographic or based on sponsor clinical trials on the product proposed for registration, an expert report should be included and cross-referenced by page number to the submission. The 'expert' should be a person with appropriate qualifications and experience who may or may not be employed by the sponsor.

The expert report should include a critical appraisal of the quality of the data generated from each trial and the relevance of the results with respect to the efficacy and safety of the product proposed for registration.

Where more than one indication is claimed, each indication should be separately justified in relation to the data included in the submission.

Where more than one active ingredient is included in the product, each active should be justified in terms of its inherent efficacy and safety as well as the efficacy and safety of the product as a whole (including a consideration of the pharmacodynamics and pharmacokinetics of each active in relation to the product as a whole). Refer also to the guideline [Multi-component products](#) in Chapter 4B, *Formulation*.

For adverse events, the expert report should provide an assessment of overall incidence, seriousness, causality of effects, dose-response relationship, special population subgroups such as

the elderly and patients with renal or hepatic impairment and an indication of reversibility or otherwise.

Guidance on the content and format of an expert report may be found in The notice to applicants, Volume 2B: Presentation and content of the dossier of the rules governing medicinal products in the European Union.

‘Generic’ products

Medicines that are essentially similar to an ‘innovator product’ may be designated as ‘generics’ or ‘branded generics’. An ‘innovator’ product (also known as the ‘originator’ product) is a medicinal product authorised and marketed on the basis of a full dossier which may include chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data.

A medicinal product is essentially similar to an ‘innovator’ product, which has been approved in Australia on the basis of a full dossier, where it satisfies the criteria of:

- having the same qualitative and quantitative composition in terms of active substances,
- having the same pharmaceutical form, and
- being bioequivalent (unless it is apparent in the light of scientific knowledge that it differs from the ‘innovator’ product as regards to safety and efficacy).

Where the clinical data provided with the originator product are not ‘protected’ (Section 25A of the Therapeutic Goods Act 1989 refers), the TGA will accept applications to register ‘generic’ products without clinical data on the basis of data that demonstrate that the ‘generic’ and ‘innovator’ products are bioequivalent, or a justification that bioequivalence data are not required. The requirements for bioequivalence data and justification for not providing bioequivalence data are set out in the EU guideline, Note for guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98).

Where product details are substantially different to the ‘innovator’ product (eg. different indications or directions for use), bridging data will be required to support the difference.

In general, bioequivalence data are not required for:

- Oral immediate release tablets, capsules and suspensions containing active substances with high solubility and high permeability and where the medicinal product has a high dissolution rate, provided the sponsor submits an acceptable justification for not providing bioequivalence data in terms of Section 5.1 of the EU guideline, Note for guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98) (as above); or
- Oral solutions if the product is an aqueous oral solution at the time of administration and contains an active substance in the same concentration as an oral solution currently approved as a medicinal product, provided the excipients contained in it do not affect gastrointestinal transit, absorption or in vivo stability of the active substance eg. gastric pH changes; or
- Products for topical use provided the product is intended to act without systemic absorption when applied locally. See Topical products in this chapter for data requirements for formulation-dependent topical products; or
- Products which contain active ingredients that are not absorbed (eg. barium sulphate); or

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Circumstances where there are other ‘generic’ products on the register that have been approved without bioequivalence data or a justification for not providing bioequivalence data. This does not apply to ‘clones’ (ie. new trade names) of the originator product.

Most OTC medicines contain active ingredients that have been used in OTC medicines in Australia for many years. The safety and efficacy of such products in many different formulations has been widely accepted. Products of this type will not require bioequivalence data or a justification for not providing bioequivalence data (see point (e) above).

Bioequivalence data (or a justification for not providing bioequivalence data) are required where:

The product is for ingestion and does not fall within the definition given in points (a) or (b) (above); or

The product is an oral solution containing an excipient that may affect gastrointestinal transit, absorption or in vivo stability of the active ingredient(s); and

The ‘innovator’ product has been approved on the basis of a full dossier and there are no ‘generic’ products on the register that have been approved without bioequivalence data or a justification for not providing bioequivalence data.

A small number of more recently approved OTC products will fall into this category. Most OTC medicines will not. Information to establish whether a product is covered by point (c) can be obtained by contacting the OTC Medicines Section

**Products with a ‘new’ dosage form**

Products with different dosage forms are not ‘generics’ as defined in ‘Generic’ products above. However, by extension, the concept of essential similarity also applies to different immediate release oral dosage forms (eg. tablets and capsules) that contain the same active ingredients.

Where a product is proposed in a ‘new’ immediate release oral dosage form (eg. an effervescent tablet where only capsules are currently included in the ARTG), and the clinical data provided with the ‘innovator’ product are not ‘protected’ (Section 25A of the Therapeutic Goods Act 1989 refers), the TGA will accept applications to register the ‘new’ product without clinical data on the basis of data that demonstrate that the ‘new’ and ‘innovator’ products are bioequivalent, or a justification that bioequivalence data are not required (as stated in the EU guideline, Note for guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98)).

Where the ‘new’ dosage form has sustained release characteristics, the guideline Modified release products in Chapter 4B, Formulation, should be followed.

**Multicomponent products**

Refer to the guideline on Multicomponent products in Chapter 4B, Formulation.

**Foreign language publications**

Trials which are reported in a language other than English can usually be excluded from consideration unless there is little information available in English. Where a report(s) in another language(s) is included, then a certified translation should be provided and a full literature search in that language(s) should be conducted to avoid the possibility of bias.

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Trials in animals

Because most OTC medicines have a substantial history of use in humans, reports of trials in animals are usually not required. However, for products containing 'new' ingredients or new routes of administration or for higher than normally accepted dosages, or for use over a longer period of time (see Chapter 6B, New substances), animal trial data may be relevant.

Post-marketing experience

Where the active ingredient is included in products currently marketed in Australia it is usually not necessary to provide post-marketing data. However, if the product is not marketed in Australia it may be relevant to include details of adverse drug reaction reports from the relevant authorities and Periodic Safety Update Reports (PSURs) where available.

Topical products

Where the efficacy of the product is likely to be formulation dependent (eg. head lice preparations, surgical scrubs, skin disinfectants, topical minoxidil), the efficacy of the particular formulation proposed for registration will need to be established.

Registered OTC medicines are evaluated in terms of quality, safety and efficacy. Some topical OTC medicines have a long history of use in many different formulations and their efficacy is well accepted. Examples include salicylic acid for treatment of warts and benzoyl peroxide for treatment of acne. Efficacy data are generally not required to support the registration of such products.

The Medicines Evaluation Committee (MEC) has identified other groups of topical products where the efficacy and/or safety of the product is influenced by the formulation. In these cases, a change in non-active ingredients may affect the extent of penetration of the active substance and therefore efficacy data is usually required before the product is recommended for approval. Because OTC medicines are so diverse, the committee has advised a flexible approach in which the need for data should be determined on a case-by-case basis.

The following categories of OTCs have been identified by the MEC as being formulation-dependent in terms of efficacy and/or safety:

- Head lice preparations
- Aciclovir for treatment of cold sores
- Minoxidil
- NSAIDs
- Antibacterial hand washes, surgical scrubs and antiseptics (other than for the 'first aid' treatment of minor wounds)
- Antidandruff shampoos containing imidazole antifungals as active ingredients
- Dithranol preparations
- Products containing glyceryl trinitrate
- Terbinafine

This list will be updated by the TGA as new categories are identified by the MEC as being formulation dependent.
In most instances, the MEC has required data from clinical trials to support the registration of formulation-dependent topical products. In some cases the OTC Medicines Evaluation Section may refer an enquiry to the MEC for specific advice on a particular product.

For guidance on data requirements for locally applied/acting products, refer to the EU document *Guidelines on the clinical requirements for locally applied, locally acting products containing known constituents (CPMP/EWP/239/95 final)*.6

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6B. New substances

This chapter describes the requirements for registration of a product containing a new substance (either active or excipient) and the provisions for ‘approval’ of a new substance for inclusion in non-prescription medicines. Specific information on requirements for new active ingredients in sunscreens is included on the TGA website. The application form for a new substance can be obtained from the TGA website or the TGA Publications Office.

A ‘new’ substance is one that is not included in any product currently entered in the ARTG for supply in Australia. Because there is usually no prior experience with the use of the substance in Australia, information is required to ensure the safety of the substance under its conditions of use.

In some circumstances, these requirements will also apply when a new route of administration is proposed for an existing substance (eg. when an excipient that is only included in topical products is proposed for use in an oral product).

In most instances a new substance will be included in a product and the application will be for registration of the product. However, the TGA is willing to accept an application for ‘approval’ of a substance in isolation from a product. In these circumstances, the safety of the substance per se will be assessed and the sponsor advised in general terms of its acceptability or otherwise for use in non-prescription medicines. Future applications to register or list non-prescription medicines containing the substance will not usually need to include data to establish the safety of the substance.

A new substance may be approved with conditions for use by a specific route of administration, and up to a maximum concentration, consistent with the data provided with the application. Further data and approval will be required if it is proposed to use the substance by a different route of administration or in higher concentrations than have been approved.

Data requirements

Toxicological studies in support of an application for a new substance should be carried out using the substance in the chemical form (eg. a salt or an ester) intended for use in the marketed product. Variations in form should be justified. Information on the regulatory status of the new substance in other countries should be provided, noting if an application for approval has been rejected or withdrawn prior to approval or withdrawn (eg. due to adverse effects) following marketing approval. Details of the approved use of the substance (eg. in therapeutic goods, food, cosmetics) and any restrictions on its approval should be provided where appropriate.

Unless it is not feasible, safety studies should be carried out in accordance with OECD guidelines of good laboratory practice (GLP – OECD Principles on good laboratory practice. Env/MC/Chem (98)17; 1998). Studies should be identified as having quality assurance from the laboratory where the study was carried out and be signed by the study director. These requirements for the conduct of a study are established practice within the EC and USA (FDA), as well as in Australia (TGA).

Representation can be made to the OTC Medicines Section to justify a data package that does not meet the requirements described in this chapter. However, the justification would need to be supported by scientific rationale (eg. an expert report) to address any omissions.

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In general, data requirements are categorised in a similar way to those for new product applications described in Chapter 6A, Efficacy and safety, based on the type of data available and experience in humans.

**Well documented substances**

Approval can be based on standard reference texts (see below) for substances with a clearly documented safety and efficacy profile and extensive experience of use in humans in other countries. Where a substance has been approved for use in foods or cosmetics in Australia or another country with a comparable regulatory system, information relating to this approval could be provided. This information should include details of approved routes of administration and acceptable daily intakes.

The following are examples of reference texts that are usually acceptable as sources of information on safety and pharmacological action/efficacy of ingredients in OTC medicines. Current editions of these texts should be used.

- Handbook of nonprescription drugs; American Pharmaceutical Association (USA)
- Clinical toxicology of commercial products; Gosselin RE et al., Williams and Wilkins (USA)
- CRC Handbook of toxicology; Derelanko MJ & Hollinger MA (Eds), CRC Press
- Meyler’s side effects of drugs; Dukes MNG et al. (Eds), Elsevier
- Martindale: The complete drug reference; Sweetman SC (Ed), Pharmaceutical Press (UK)
- Handbook of pharmaceutical excipients; Kibbe AH (ed), American Pharmaceutical Association (USA) and Pharmaceutical Press (UK)

**Substances which are not well documented**

Where the new substance is not well documented in standard reference texts, a bibliographic submission may be appropriate. Requirements for a bibliographic submission are given in Chapter 6A, Efficacy and safety. In this instance, the Register of Toxic Effects of Chemical Substances (RTECS), Toxnet (Toxline), Medline or Embase (Excerpta Medica) would be acceptable databases on which to base a literature search.

In the case of a substance where there is little or no experience of its use in humans, the safety and efficacy of the substance would be assessed on the basis of preclinical data submitted. For new active substances, data consistent with the requirements of the EU guidelines relevant to the assessment of a new chemical entity should be provided. The EU guidelines adopted by the TGA are detailed on the TGA website[^3]. Relevant guidelines can be found in the sections covering pharmacology, pharmacokinetics and toxicology.

These data requirements include efficacy/exposure studies addressing the pharmacological activity and pharmacokinetic behaviour of the substance as well as safety studies addressing acute toxicity, repeat-dose toxicity, carcinogenicity, genotoxicity and reproductive toxicity. Studies need to include clear, legible tabulation and a descriptive presentation of the findings as well as individual animal data for validation of the results.

Sponsors applying for approval of active substances which are intended for topical or dermal use should provide data on the pharmacokinetics/toxicokinetics of the substance. The kinetic studies should include information on absorption, distribution, metabolism and excretion of the substance and any active metabolites for both the oral and intended route of administration.

All toxicity studies should use a high enough dose to generate meaningful data (precipitate toxicity), with dose selection based on the Maximum Tolerated Dose (MTD). Interpretation of toxicity studies relies on comprehensive kinetic data to determine whether any lack of toxicity is due to a low intrinsic toxicity of the test material or to poor absorption of the substance from the gastrointestinal tract or through the skin.

The data requirements described above are flexible and not prescriptive. Approval may be based on the evaluation of a data package containing elements from each data category (e.g., references in textbooks plus a journal article and a reproductive toxicity study) provided omissions/variations are justified in an expert report.

A number of countries (USA, Canada, Sweden, The Netherlands and the UK) have similar regulatory systems to Australia for the evaluation of new substances. Where a substance has been evaluated in a country with a similar regulatory system to Australia, evaluation reports from one or more of these countries can form the basis of an application for approval by the TGA.

The sponsor should submit all relevant and appropriate data (company and contract laboratory studies, published literature, etc) on the substance. Full copies of all cited references should be submitted to enable validation of the methodology and results. Studies which were carried out pre-GLP may not be suitable for evaluation. Information from Periodic Safety Update Reports (PSURs) may be included.

Certified English translations should be provided for all non-English language references or studies.

**Chemistry requirements**

In addition to data to establish the safety of the proposed new substance, the sponsor should provide data establishing the chemical identity of the substance. A full description of the substance, including its chemical structure, physical properties, CAS number, molecular weight, molecular formula and nomenclature should be provided, where appropriate. This should include data indicating whether the substance is a derivative of a known chemical compound, or a number of well characterised series of chemical compounds.

The following data should be provided in relation to the proposed new substance:

- The chemical ‘fingerprint’ of the substance – this could be in the form of chromatographic data (Thin layer chromatography (TLC), High performance liquid chromatography (HPLC), etc), and spectra;
- Assay procedures for the general identity criteria – references or a detailed description of the procedure should be provided;
- Test methods, specifications and results of relevant tests for microbiological, chemical, foreign matter, residues, etc, sufficient to establish product purity, should also be provided.

For a new active substance, information concerning the stability of the substance before and after incorporation into the product(s) proposed for sale should be provided, where applicable. This should include any effects of mixing with other substances and incorporating into different dosage forms, where applicable. Storage trial data should be provided where available.
7. Review of decisions

The Medicines Evaluation Committee – ‘opportunity to be heard’

Where an application is under evaluation by the MEC and it appears that rejection is to be recommended, the committee has established a procedure whereby the sponsor is invited to appear at a committee meeting and present a submission in support of the application.

This is not a formal appeal mechanism but is simply a means of ensuring that you have an opportunity to personally present a case to the committee. It has no bearing on any subsequent right of appeal to the Minister or Administrative Appeals Tribunal if the application is rejected.

If your application is formally rejected by the TGA you will be sent a letter from the Delegate of the Secretary informing you of the decision and setting out the reasons for the rejection. If you wish to have this decision reviewed, a number of procedures are available (section 60 of the Act refers).

Reconsideration by the Minister

In the first instance you may write to the Minister, within 90 (calendar) days of receiving the rejection letter, requesting a reconsideration of the decision to reject the application. Directions on how to proceed will be given in the rejection letter. The decision is generally reviewed by a delegate of the Minister, usually a senior officer of the TGA other than the officer who made the initial decision.

After the decision has been reviewed, you will be given a statement of the outcome and, if the decision is confirmed, advice on further options available to you. The delegate of the Minister may confirm the initial decision or revoke it and substitute another decision in its place. If you do not receive notice of the review of the decision within 60 (calendar) days of your request it is taken that the initial decision is confirmed.

The Administrative Appeals Tribunal

If you are dissatisfied with the results of the reconsideration you may then make an appeal to the Administrative Appeals Tribunal for a review of the decision.
8. Post marketing surveillance

Products which are already being marketed are subject to a number of levels of surveillance by the TGA.

**The sampling program**

The TGA Laboratories undertake a continuous sampling program in all states of Australia. Products are purchased in the marketplace, or obtained from manufacturers or sponsors, and subjected to analysis and regulatory scrutiny. Products not meeting the required standards may be subject to corrective action, recall or removal from the register.

**Good Manufacturing Practice (GMP) audits**

Manufacturers of therapeutic goods in Australia are subject to regular inspections by the TGA’s Manufacturer Assessment Section. Details of requirements for manufacture are specified in the *Australian Code of Good Manufacturing Practice* for medicinal products\(^1\).

The evaluation committees may request that particular problems encountered during the evaluation process be followed up with the manufacturer during subsequent GMP audits.

See also [Post-registration requirements](#) in Chapter 4E, *Stability testing*.

**‘Grandfathered’ products**

Those products entered in the ARTG under the ‘grandfather’ provisions of the Act may be subject to future evaluation to determine whether they should remain on the Register. If you are the sponsor of such a product, you should ensure that you hold evidence to substantiate the quality, safety and efficacy of the product. You should also ensure that an ongoing stability testing program is in place for each product under your control.

**The Surveillance Unit**

The Surveillance Unit investigates breaches of the legislation and coordinates prosecutions.

**Problem reporting and recall**

Recalls of therapeutic goods are coordinated by the TGA’s Recalls Section. Information can be obtained from the TGA website\(^2\).

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9. MEC guidelines

This Chapter represents a summary of the views of the TGA and the Medicines Evaluation Committee (MEC) with respect to OTC medicines (including new substances) at the time of publication and is intended to assist sponsors in submitting acceptable applications for registration of OTC medicines.

Products are assessed according to the best clinical and scientific information at the time of evaluation. If you believe that a particular application warrants a departure from the Guidelines, a justification should be submitted with the application.

The guidelines are not mandatory for existing products. However sponsors of existing products are encouraged to update labels to comply with the relevant guidelines when submitting label variation applications (refer to Chapter 11, Changes to OTC medicines, for information on changes to existing products).

Suggested statements (for labelling purposes) are written in this chapter of the guideline as dot points and in italics. Comments relating to these suggested statements are in normal font and are not intended for inclusion on the labels.

Allantoin

The absence of convincing evidence that allantoin has a role as a wound healing agent precludes any claims being made for its efficacy in this regard.

Alpha hydroxy acids

There is evidence to suggest that the use of topical products containing alpha hydroxy acids (such as glycolic acid, lactic acid, citric acid and other fruit acids) may make users more sensitive to sunlight and especially to the ultraviolet (UV) radiation component of sunlight. UV exposure can damage the skin and at high doses, especially over a long period, can cause skin cancer (refer to the FDA Backgrounder – Alpha Hydroxy Acids in Cosmetics, 3 July 1997).

The following statements should be included in the labelling of products containing alpha hydroxy acids:

- This product may make your skin more sensitive to sunlight;
- Sun exposure should be limited by using a sunscreen and by wearing protective clothing;
- If you have sensitive skin, test this product on a small area of skin before applying it to a large area;
- Transient stinging or irritation may occur when using this product. If irritation persists, discontinue use; and
- Not recommended for use on children or infants.

Anaesthetics, dermal

All products containing local anaesthetics for dermal use must contain a statement such as:

If irritation occurs, stop use immediately and seek medical advice.

1 http://vm.cfsan.fda.gov/~dms/cos-aha.html
Antacids, liquid

This guideline is currently under review.

Liquid antacids are susceptible to microbiological contamination and deterioration of flavour and fragrance after the container is opened. Experience also indicates that some patients, contrary to the manufacturer's advice, swig the medicine directly from the bottle. Liquid antacids should either comply with the TGA guidelines in Chapter 4F, Microbiological testing, throughout the life of the product in both opened and unopened containers, or have a statement on the label to discard the contents ‘x’ months after opening the bottle. Space could be provided for the user to write the date of first opening.

Anthelmintics

Product labels should contain statements such as:

- A common symptom of threadworm infestation is itching around the anus and vagina, which may result in restless sleep and irritability.
- Evidence of infestation should be present before treating for threadworm.
- If a family member has threadworms, then each member of the family should be treated.
- If symptoms persist, see your doctor.

Label copy should not encourage the regular use of anthelmintics.

Antifungal agents, topical

The prophylactic use of topical antifungal agents, including application to shoes or clothing, should be justified. Because fungal infections may recur if treatment is stopped as soon as symptoms disappear, the label should state that it is preferable that the product should be applied for 14 days after symptoms disappear.

It is recognised that in some circumstances, such as communal showers and tropical climates, a topical antifungal agent may be used more freely but the directions for use should set out the relevant circumstances.

Antihistamines

Use in respiratory tract infections

Any claim that implies that antihistamines are useful for lower respiratory tract conditions (including infections and asthma) should be justified with clinical data.

Use as hypnotics

Antihistamines (H1 receptor antagonists), especially ethanolamines (eg. doxylamine, diphenhydramine) or phenothiazines (eg. promethazine) have hypnotic properties. In general, sleep disorders should be medically assessed, as they may be symptomatic of more serious conditions such as depressive illness. The use of non-medically prescribed hypnotics is therefore not encouraged.
Sponsors of products containing antihistamines that are indicated for short-term use in occasional insomnia will be expected to:

- limit the pack size to not more than 10 doses;
- state on the label that the product should be taken on medical or pharmacist advice, that it is for temporary use and that it is to be avoided during pregnancy or lactation;
- include a warning about driving and the morning-after effect consistent with the Standard for uniform scheduling of drugs and poisons (SUSDP) Appendix F warning statement no. 90 (the product may have a carry-over effect the next day);
- include in the Consumer Medicine Information, package insert or label the following principles of good sleep hygiene:
  - go to bed and arise at the same time daily;
  - engage in relaxing activities before bedtime;
  - exercise regularly but not in the late evening;
  - avoid eating meals or large snacks just before bedtime;
  - eliminate daytime naps;
  - avoid caffeine-containing drinks after midday;
  - avoid alcohol or the use of nicotine late in the evening;
  - minimise external disruption (eg. light and noise);
  - if you are unable to sleep, do not become anxious; leave the bedroom and participate in relaxing activities such as reading or listening to music until you are tired.

See also Paediatric products

**Aspartame**

Aspartame is a sweetening agent based on the essential amino acid phenylalanine which is normally metabolised to tyrosine. The enzyme required for this metabolism is lacking in people with phenylketonuria.

Medicines containing aspartame or phenylalanine should include the warning in bold:

PHENYLKETONURICS: CONTAINS PHENYLALANINE.

**Aspirin**

**Indications**

**Analgesia**

Sponsors may use any or all of the representative indications set out below (or similar) as appropriate to a particular product without the need to supply supporting efficacy data:

For the temporary relief of pain (and discomfort) associated with headache, migraine headache, toothache, dental procedures, backache, arthritis, rheumatics, period pain, fibrositis, neuralgia, sore throat, and the symptoms of cold and flu. Reduces fever. Relieves inflammation associated with muscular pain, strains and sprains.

Sponsors may propose other indications but should contact the OTC Medicines Evaluation Section for advice on whether data will be required to support the safety and efficacy of the product for those indications.

As fever is a normal and beneficial response to infection, no elaboration to the words “reduces fever” will be accepted except in the context of limits to the duration of the treatment and with regard to the relief of discomfort associated with fever.
Antiplatelet
When the product is also indicated as anticoagulant therapy, the following statement should be added to the Indications section of the Product Information document:

For the treatment of patients with known cardiovascular or cerebrovascular disease, as an antiplatelet agent for prophylaxis against acute myocardial infarction, unstable angina, transient ischaemic attack and cerebrovascular accident (stroke).

For cardiovascular system claims, an exemption is required under Regulation 9 of the Therapeutic Goods Regulations.

Warning Statements
Warning statements must be included on the label as specified in the Standard for the uniform scheduling of drugs and poisons (SUSDP). In addition, the following statements (or words to that effect) should be included on the label or on a package insert:

- Do not use in the presence of asthma, a stomach ulcer, if you are pregnant or if you are taking anticoagulant medication (unless advised by your doctor). Do not take if you are allergic to aspirin.

Dose
Analgesia
Adult dosage recommendations (adults and children over 12 years):

300 mg to 1000 mg every four hours as necessary. Dosage should not exceed 4 g (expressed on the label as the number of units, eg. tablets) in 24 hours for not more than 10 days.

Antiplatelet
The dosage instructions on the label should include the statement:

- As an antiplatelet agent (only on medical advice): 75-325 mg per day.

Combination products
Products containing more than one active ingredient which are similar to existing registered products will usually not require efficacy or safety data, provided they comply with the guideline on Multi-component products (in Chapter 4B, Formulation). Where new combinations are proposed (ie. combinations and/or strengths that are not included in the Australian Register of Therapeutic Goods for supply in Australia), the safety and efficacy of the combination will need to be justified.

Where aspirin is used in combination with other active ingredients, the indications listed above for aspirin may be appropriate for the combination product subject to compliance with the guideline on multi-component products.

Bath Oils
Oily products intended for use in the bath may cause the bath to become slippery or, when used in a baby’s bath, may cause the baby to become slippery. Products of this type should contain a label warning statement such as:

- Caution: Use of this product may cause the body and bathroom surfaces to become slippery. Particular care should be exercised when handling a baby.
Benzocaine

See Anaesthetics, dermal

Benzoyl peroxide

Labels of both scheduled and unscheduled products containing benzoyl peroxide should include the statements specified in the Standard for uniform scheduling of drugs and poisons (SUSDP)\(^2\) for products containing benzoyl peroxide when included in ‘Pharmacy Medicine’ (Schedule 2) – Appendix F warning statement no. 55.

Bronchitis, use of term

Bronchitis is an inflammation of the mucous membranes of the bronchi. The condition is serious and complications can be severe. Products which offer symptomatic relief should not include the word bronchitis as part of the product’s name, and should not include the word bronchitis on the labels other than in the context of a statement such as:

- For the relief of cough of bronchitis. If the cough persists, seek medical advice.

Burn treatment products

Labels should indicate that immediate treatment should consist of the rapid application of cold water or cold packs for at least 20 minutes and that the product should only be applied later. Ice should not be applied directly to the burnt area.

Directions for use should indicate clearly that the product is for the first-aid treatment of minor burns only and that medical advice should be sought for the treatment of more serious burns.

Caffeine

Reservations are held about the use of caffeine as a stimulant or alerting agent in medicines. All such preparations are required to have the following adult dose:

- 100 mg per dose maximum, which may be repeated at three hourly intervals. Do not exceed 600 mg in 24 hours.

The label should state that the dose should be reduced if tea, coffee or other products containing caffeine are taken.

The use of caffeine in weight control preparations is considered unsuitable.

Calcium supplements and osteoporosis

The labelling of calcium products intended for use in the prevention and treatment of osteoporosis is to imply only that the product may be of assistance in the prevention and adjunctive treatment of osteoporosis.

The labels of such products should include a statement such as:

- Check with your prescriber or pharmacist if you are taking other medicines for osteoporosis.
Camphor

The directions for use for dermal preparations containing camphor should indicate that the product is not to be applied to infants under 12 months of age unless on the advice of a physician.

In the absence of clinical evidence to support the inclusion of camphor in steam inhalant solutions, registration of such products will not be approved.

See also Chest rubs

Cetrimide

Adverse reactions have been reported following repeated application of creams containing more than 1% cetrimide. Products of this nature will generally not be approved for registration.

Chest rubs

The use of chest rubs will not be accepted for the treatment of bronchial conditions. The only statement of indications that will be accepted for chest rubs containing ingredients such as eucalyptus oil, menthol, camphor and other aromatics is:

- *May relieve the nasal congestion of colds and make breathing easier (or similar wording).*

The directions for use for chest rubs should indicate that the product is not to be applied to infants under 12 months of age unless on the advice of a physician.

See also Camphor, Eucalyptus oil and Use of the term ‘easy breathing’ (Chapter 5B, Labelling)

Coal tar preparations

*Guideline amended 13 February 2004*

All coal tar preparations contain mutagens and are potentially carcinogenic. Justification for the inclusion of coal tar in terms of benefit versus risk should be provided. Indications for use in minor conditions (e.g. napkin rash) will not be accepted.

Because of the potential for increased absorption associated with the use of coal tar under occlusive dressings, a warning should be included on the product labelling (and Consumer Medicine Information (CMI) and Product Information (PI) where these are provided), such as:

- *Not to be used under occlusion except on medical advice.*

The use of a light bandage to prevent staining of clothes is acceptable.

This advice need not be included on the labelling of shampoos or other products which are designed to be washed off after application.

Since the safety of coal tars on children under 2 years of age has not been established, the labelling (and CMI and PI where these are provided) of all topical products containing coal tar should also include a warning such as:

- *Not recommended for use on children under 2 years of age except under the direction and supervision of a physician.*

Although no human data are available on the effects of using coal tar during pregnancy or lactation, the presence of mutagens in the urine has been reported following topical application of coal tar.

The labelling (and CMI and PI where these are provided) of all topical coal tar preparations should include a warning, such as:

- Not recommended for use during pregnancy or while breastfeeding.

**Codeine**

*Guideline added 28 June 2006*

The Product Information (PI) of codeine-containing products should include:

- Under ‘Pharmacokinetics’ (‘Metabolism’): A statement advising that about 8% of patients metabolise drugs poorly via CYP2D6, and are likely to obtain reduced pain relief from codeine due to reduced formation of the active metabolite, morphine (note: the ‘Pharmacokinetics’ section of the PI should specifically state that codeine’s active metabolite is morphine); and

- Under ‘Precautions’ – ‘Interactions with other drugs’: A statement advising of the possibility of interactions between codeine and drugs that can inhibit CYP2D6, such as quinidine, phenothiazines and antipsychotic agents.

The Consumer Medicine Information (CMI) of codeine-containing products should advise that about 8% of people are poor metabolisers of codeine, and that poor metabolisers are likely to obtain reduced pain relief with codeine compared with other people who are not poor metabolisers.

**Colouring agents**

*Deleted 25 June 2004*

**Corn treatments**

Statements such as the following should be included in labels:

- Do not use if you have diabetes or impaired circulation.

- Do not use on infants or very young children unless on medical advice.

**Corticosteroid nasal sprays**

Certain low dose aqueous corticosteroid nasal sprays are scheduled as OTC medicines. Restrictions on dose, pack size and indications are included in the relevant Schedule entry in the *Standard for the uniform scheduling of drugs and poisons* (SUSDP).

In addition to the requirements of the Labelling Order, the label should include information on warnings, contraindications, precautions, and adverse effects. Alternatively, this information could be included in a Consumer Medicine Information (CMI) leaflet provided with the product.

The following, or words to the effect, should be included either on the label or the CMI leaflet:

- Do not exceed the maximum stated dose

- A lower maintenance dose should be used once full effect is obtained

- Do not use for more than 6 months without the advice of your doctor or pharmacist

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• See your doctor or pharmacist before using this product if:
  - you have a nasal or sinus infection;
  - you have recently had an injury or surgery to your nose;
  - you have ulceration in your nose.

• See your doctor or pharmacist if:
  - symptoms are not relieved within 7 days;
  - your nose bleeds;
  - you develop signs or symptoms of a nasal or sinus infection such as fever, pain or swelling, or discoloured nasal discharge;
  - you have eye pain or visual disturbances.

Where the information is included in the CMI leaflet, the label should include a statement such as:

• Read the enclosed Consumer Medicine Information leaflet before starting to use this product.

**Decongestant products, nasal**

Rebound nasal congestion can occur as a result of continued use of topically administered decongestant nasal products. Such products should contain a statement such as:

• *If congestion persists for more than a few days, seek medical or pharmacist advice.*

**Decongestant products, oral**

**Sympathomimetic amines**

Because of the unpredictable effect that sympathomimetic amines (eg. pseudoephedrine, phenylpropanolamine) may have on blood pressure and the risk of interactions with antidepressant medication, products should contain a warning statement such as:

• *See your doctor before taking this product if you have high blood pressure or heart problems or are taking antidepressant medication.*

Pseudoephedrine is a stimulant of the central nervous system and may cause sleeplessness if it is taken up to several hours before going to bed in susceptible people, therefore, a warning should appear on the label such as:

• *Pseudoephedrine may cause sleeplessness if it is taken up to several hours before going to bed.*

If the product contains a sedating antihistamine, this warning may be omitted at the discretion of the Medicines Evaluation Committee. Clinical evidence would be required to indicate that sleeplessness does not occur.

**Diarrhoea treatments**

Labels for all products should include a statement such as:

• *If diarrhoea persists, seek medical advice.*

**Infants under 6 months**

Diarrhoea which persists for longer than six hours requires medical attention because of the life-threatening consequences of dehydration.
Children under 3 years of age

Medical consultation is preferable to home treatments. Oral rehydration products, however, can serve a useful role in reducing the consequences of diarrhoea in this age group.

Children from 3 to 6 years

Should be treated for diarrhoea for only short periods before medical advice is sought.

The directions for use on product labels should include the following:

<table>
<thead>
<tr>
<th>Age of child</th>
<th>Additional directions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Under 6 months</td>
<td>Medical advice should be sought if diarrhoea persists for more than 6 hours.</td>
</tr>
<tr>
<td>Under 3 years</td>
<td>Medical advice should be sought if diarrhoea persists for more than 12 hours.</td>
</tr>
<tr>
<td>3-6 years</td>
<td>Medical advice should be sought if diarrhoea persists for more than 24 hours.</td>
</tr>
<tr>
<td>Over 6 years</td>
<td>Medical advice should be sought if diarrhoea persists for more than 48 hours.</td>
</tr>
</tbody>
</table>

The Consumer Medicine Information (CMI) or label should include a description of the symptoms of dehydration for the benefit of consumers.

Oral rehydration salts should be labelled and formulated to conform to the recommendations of an accepted authority (e.g., the British Pharmacopoeia, World Health Organisation). Other formulations will be considered but must be justified.

Where inorganic adsorbing agents (such as kaolin) are included in a formulation, evidence should be included to show that any other active ingredient is not irreversibly adsorbed or inactivated by the agent. In the absence of supporting clinical data, simple adsorbent preparations for the treatment of diarrhoea will not be registered.

It is considered that there is insufficient evidence to support the use of solanaceous alkaloids in the treatment of diarrhoea in adults or children.

Ear drops

Current medical opinion indicates that the use of ear drops be limited to:

- the prevention or treatment of medically diagnosed otitis externa; or
- the treatment of ‘swimmer’s ear’; or
- wax softening (wax softeners should be bland and non-irritating).

In cases of ear perforation (or where there is a likelihood of ear perforation) or where grommets (ventilation tubes) are present, medical advice should be sought before ear drops are used.

Applications for registration of an ear drop containing a local anaesthetic should be accompanied by evidence of safety and efficacy.
Electrolyte replacement products

Electrolyte replacement products should be labelled and formulated to conform to the recommendations of an accepted authority (eg. the British Pharmacopoeia, World Health Organisation). Other formulations will be considered but must be justified.

Eucalyptus oil

Eucalyptus oil should not be used in oral preparations (other than as a flavouring agent) because of its toxicity and lack of therapeutic benefit.

In the absence of clinical evidence to support the inclusion of eucalyptus oil in steam inhalant solutions, registration of such products will not be approved.

See also Chest rubs

Expectorants

In the absence of proof to the contrary, guaifenesin is the only substance recognised as an expectorant. Sponsors wishing to use this term for any other ingredient should provide clinical data to support the claim.

Eye preparations

The Labelling Order5 made under the Therapeutic Goods Act 1989 requires a statement on the label that eye preparations must be discarded four weeks after the date of initial opening. Consumers will be assisted if space is provided on the label for the user to write the date when the container is first opened.

Consideration should be given to the possibility of interactions between eye preparations and contact lens materials, and a suitable statement should be included on the product label where appropriate.

Vasoconstrictor eye drops

Following advice from the Royal Australian College of Ophthalmologists, warnings to the effect of the following are required to be included on the primary pack or package insert of vasoconstrictor eye drops:

- *Prolonged use may be harmful*
- *Consult a doctor or pharmacist if using other eye products.*
- *Do not use if you have glaucoma or other serious eye conditions.*
- *If symptoms persist, consult a doctor.*

The indications for use should not include references to close work, tiredness, driving or similar non-specific claims.

The product name and label text should not encourage inappropriate use for trivial or cosmetic purposes. References to ‘soothing’ or ‘whitening’ in the presentation of the product will not be accepted.

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Family packs

The term ‘family packs’ refers to products that are indicated for use both in adults and children. In general, products in solid dosage forms (eg. tablets, capsules) should not be labelled for use in young children because of the danger of inhalation. Where other presentations more suitable for use in young children are available, the dosage instructions on the label of the solid dosage form should include advice as to the availability of these other presentations. Where such presentations do not exist, sponsors should consider developing alternative presentations that are more suitable for children.

If no specific presentation is available and the product is indicated for use in children, the label should include appropriate dosage instructions for use in children. If the labels of solid dose form products indicate that they can be used “for the whole family”, and if appropriate and the formulation permits, the label should also advise that the tablets should be crushed or capsules emptied and the contents mixed with water, jam or honey before administering to young children or any individual who has difficulty swallowing tablets or capsules.

Fluoride-containing preparations

Products should comply with NHMRC recommendations presented in Report of the working party on fluorides in the control of dental caries, November 1985. The Council recommended that in areas with less than 0.3 ppm of fluoride in the domestic water, dietary fluoride supplements should be taken as specified in the table which follows:

<table>
<thead>
<tr>
<th>Age</th>
<th>Daily fluoride supplement</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 weeks to 2 years</td>
<td>0.25 mg</td>
</tr>
<tr>
<td>2 to 3 years</td>
<td>0.5 mg</td>
</tr>
<tr>
<td>3 to 16 years</td>
<td>1.0 mg</td>
</tr>
</tbody>
</table>

The NHMRC is currently reconsidering their dosage recommendations for fluoride supplements. Dosages recommended in this guideline will be amended to remain consistent with NHMRC recommendations.

While there is some evidence indicating that the use of fluoride supplements during pregnancy may give some protection against dental caries of the offspring, the weight of evidence does not support the use of such supplements. However, there is no contraindication to a pregnant woman living in a non-fluoridated area taking fluoride supplements.

Product labels should contain a statement such as:

- Contact your dental professional or local water authority for information on the fluoride content of your water supply.

Haemorrhoidal treatments

Product labels should contain a statement such as:

- If symptoms persist, seek medical advice.
Head lice treatment products

See Insecticidal products – Head lice treatment products

High fibre products

Products with a high fibre content should include a statement such as the following on the label:

- High fibre products may interact with other medicines by altering their absorption. Check with your doctor or pharmacist if taking other medicines.

Where a Product Information document is to be used it should include a statement such as the following:

- High fibre products have the potential to interact with other medications by altering their absorption. Close monitoring of the effects of medications may be necessary for patients who commence or cease to take this product regularly.

See also Laxatives

Hydroquinone

The hyperpigmentation caused by pregnancy is self-limiting and should not be treated with hydroquinone. This indication will not be permitted for preparations containing hydroquinone.

Labels of products containing hydroquinone should include the statements required by the Standard for uniform scheduling of drugs and poisons (SUSDP) – Appendix F warning statement no. 45.

The following warning should also be included on the labelling of products containing hydroquinone:

- Long term and repeated use should be avoided because darkening of the skin could occur.

Other substances in the formulation may enhance the absorption of hydroquinone. Sponsors should take this into account in formulating products and address this issue as part of the registration application.

Hypoallergenicity of topical preparations

Where a product contains a claim of hypoallergenicity, evidence must be provided that the product has been tested and found to pass a suitable test such as the Kligman Maximisation Test or an internationally recognised alternative for irritation and sensitisation. Repeat Insult Patch Testing (RIPT) is not a suitable substitute as it is not conducted in a system that has magnified responsiveness as would be encountered in a sensitive individual.

Ibuprofen

Indications

Sponsors may use any or all of the representative indications set out below (or similar) as appropriate to a particular product without the need to supply supporting efficacy data.

The temporary relief of pain (and discomfort) associated with headache, migraine headache, tension headache, sinus pain, toothache, dental procedures, backache, muscular aches and pains, period pain, sore throat, tennis elbow, arthritis, rheumatic pain and the aches and pains associated with colds and flu. Reduces fever.
For paediatric formulations, teething, earache and immunisation may be added to any of the above, as appropriate to the age group.

Sponsors may propose other indications but should contact the OTC Medicines Evaluation Section for advice on whether data will be required to support the safety and efficacy of the product for those indications.

As fever is a normal and generally beneficial response to infection, no elaboration to the words “reduces fever” will be accepted except with regard to the duration of treatment or relief of discomfort associated with fever or to give examples of conditions in which fever may occur.

**Warning statements**

Warning statements should be included on the label as specified in the *Standard for the uniform scheduling of drugs and poisons* (SUSDP).

In addition, the following statements (or words to that effect) should be included on the label or on a package insert:

For both orally and topically administered products containing ibuprofen:

- *Ask your doctor or pharmacist before use if you have asthma.*

- [If desired this could be replaced with a statement such as: Most asthmatics can take/use products containing ibuprofen, but if you are sensitive to ibuprofen, aspirin or other medicines for pain relief, do not take this product. If you are unsure, consult your pharmacist or doctor.]

- *Do not take/use if you are allergic to aspirin, ibuprofen, or other medicines for pain relief.*

For orally administered products containing ibuprofen:

- *Do not use in the presence of a stomach ulcer or other stomach disorders, impaired kidney function or heart failure.*

- *Ask your doctor before use if you are pregnant or are taking anticoagulant medication, medication for high blood pressure, diuretics, lithium, methotrexate or other medicines for pain relief.*

**Dose**

Adult dosage recommendations (adults and children 12 years and over):

200 mg or 400 mg initially taken with fluid, then 200-400 mg every four to six hours as necessary. Dosage should not exceed 1200 mg (expressed on the label as number of units, eg, tablets) in 24 hours.

Paediatric dosage recommendations (6 months to 12 years):

The recommended paediatric dose is 5-10 mg/kg/dose. Doses should be given every 6-8 hours as necessary with no more than four doses in 24 hours.

Where dosage instructions for children under 12 months of age are included on the labelling, the dosage instructions must include statements advising that the product should not be given to infants under 6 months, and that it should only be given to infants aged 6-12 months following the advice of a doctor.
Doses should be expressed where possible in whole numbers and should be presented with age, weight and volumes (in mL) unless otherwise justified.

If desired, wider age ranges could be used on product labelling (e.g. 1-3 years). Labels could include appropriate discrete doses (consistent with the above table), instead of dosage ranges.

The recommended dose should be able to be measured using commonly available metric measuring devices. There may be instances, therefore, where the dose needs to be slightly different from the recommended milligram doses given above, depending on the ibuprofen concentration of the product, or dosing device provided with the product.

Sponsors intending to supply measuring devices with the product should consult Australian Standard AS 2224.2 – 1986. Calibrations on measuring devices should be exclusively in metric units and correspond with the doses shown on the label where possible to minimise the need for calculation and guesswork.

Dosage instructions could include advice consistent with the following:

*If you know your child’s weight, choose a dose for that weight rather than the dose given according to the child’s age.*

Dosage instructions could also advise that if the child weighs more than 41 kg, they should be dosed at a rate of 5-10 mg/kg body weight per dose with a maximum single dose (for any age) of 400 mg, and a maximum daily dose of 1200 mg.

Paediatric dosage recommendations – solid dose products (children 7 to 12 years only):

Recognising that dosing with solid dose products is less flexible than with liquid products, solid dose products could include a dose of 200 mg every 6-8 hours as necessary, with no more than four doses in 24 hours, for children aged 7-12 years.
Combination products

Products containing more than one active ingredient which are similar to existing registered products will usually not require efficacy or safety data, provided they comply with the guideline on Multi-component products (in Chapter 4B, Formulation). Where new combinations are proposed (ie. combinations and/or strengths that are not included in the Australian Register of Therapeutic Goods for supply in Australia), the safety and efficacy of the combination will need to be justified.

Where ibuprofen is used in combination with other active ingredients, the indications listed above for ibuprofen may be appropriate for the combination product subject to compliance with the guideline on multi-component products.

See also Paediatric products

Insecticidal products

Head lice treatment products

Guideline amended 1 December 2003

Evidence suggests that the efficacy of head lice treatment products is formulation dependent. Sponsors of new products should provide data to support the efficacy of their specific formulation when used according to the directions for use on the product's label.

The efficacy and safety of head lice products should generally be supported by relevant clinical trials, rather than in vitro data only. In vitro data may be acceptable, at the discretion of the evaluation body, where the formulation of a product is similar to an existing product that has been fully evaluated.

Efficacy data should ideally consist of clinical trials conducted in Australia, to address location-specific resistance issues. Claims for registered products must be limited to control/treatment of head lice and their eggs (except see below regarding prophylactic use). Since no pediculocides have been shown to be 100% insecticidal and ovicidal under all conditions of use, claims must not state or imply that one treatment can kill all lice and their eggs.

Sponsors must not claim prophylactic use (preventative or repellent action) as an indication unless they can provide satisfactory evidence that such use of the product will not promote the development of resistance. Safety and efficacy of prophylactic use must also be supported by clinical trial data.

The use of lindane and benzyl benzoate in products registered for the treatment of head lice infestation is discouraged.

Labels and / or package inserts should include the following statements (or words to that effect) immediately after the dosage instructions:

1. Use enough to thoroughly cover the scalp, including the back of the neck and behind the ears.
2. If the product gets into the eyes, rinse out immediately with water.
3. Remove all the eggs (nits) you can find after treatment (this is easier with a fine tooth comb and hair conditioner on wet or dry hair)
4. Repeat the treatment after 7-10 days to kill lice that have hatched from any remaining eggs that were not killed by the first treatment.
5. If you find live lice or more eggs appear after the second treatment, seek advice from a health care professional.
6. Only use the product when you can see live lice or their eggs. Don’t use regularly or to prevent head lice.
7. Check other people in the household and treat if necessary. Lice can quickly spread back to people who have already been treated.

8. Don’t use on babies under 6 months, except on medical advice.

Consistent with requirements for other OTC products, the labels of pediculocide products containing active ingredients with an ADEC pregnancy category other than Category A should include a warning to the effect that the product should not be used in pregnancy unless advised by a doctor. This includes products containing malathion, pyrethrins or permethrin (in category B2), and products containing piperonyl butoxide (category B3).

Because education is an important component of treatment, sponsors are encouraged to make available relevant public health information on the treatment of head lice infestation in a package insert, a web site referenced on the label or by other means (eg. a telephone information service).

**Lindane for therapeutic use**

Questions have been raised concerning the safety of the use of lindane for the treatment of head lice, body lice, crab lice, and scabies infestations. Serious adverse reactions to products containing lindane may result from the incorrect use of products. However, evidence from the literature shows that it has been used safely and effectively in millions of patients.

While applications for the registration of new products containing lindane are unlikely, it is important to maintain access to these products for use in treatment of Norwegian scabies or in case of resistance to other agents.

Products containing lindane must contain warning statements to the effect of the following:

- This preparation must not be used on broken skin; and

- This preparation should be used with caution on infants, small children and pregnant or lactating women. Medical advice should be sought before use.

**Iodine**

See [Povidone-iodine/iodine – dermal](#)

**Kaolin**

See [Diarrhoea treatments](#)

**Laxatives**

The correct management of uncomplicated constipation consists of correct diet, adequate fluid intake and suitable exercise. In cases where occasional treatment is required, the use of bulking agents is viewed favourably.

Product labels should contain the following advice:

- Drink plenty of water;

- Increase fibre in diet except in cases of medication-induced constipation (eg. with codeine);

- Prolonged use of laxatives is undesirable and may lead to dependence (this advice does not apply to bulk forming agents); and

- If symptoms persist seek medical advice.

Weight reduction claims will not be approved for products containing laxative ingredients.
The use of the term ‘gentle’ will not be approved in relation to products containing a stimulant laxative (eg. senna, bisacodyl).

Products containing senna, aloe or cascara should contain a label statement such as:

- Do not use when abdominal pain, nausea or vomiting is present. If you are pregnant or breast feeding, seek medical advice before taking this product.

Products containing purgative ingredients, such as jalap, podophyllum or wahoo, are not regarded as acceptable therapy for the treatment of simple constipation.

This guideline applies to any laxative product, including oral dose forms, enemas and suppositories.

See also [High fibre products](#)

### Lignocaine

See [Anaesthetics, dermal](#)

### Lindane

See [Insecticidal products – Lindane](#)

### Lozenges

#### Anaesthetic lozenges – use in children

Label copy for lozenges containing a local anaesthetic for the relief of the pain and discomfort of sore throats and after minor dental procedures must indicate that the product is not to be taken by children under six years of age, unless recommended by a physician, pharmacist or dental professional.

#### Anaesthetic lozenges – strength of local anaesthetic

Anaesthetic throat lozenges have a short duration of action and consumers may self-administer the product more frequently than recommended on the label.

The dose of local anaesthetic should be the lowest efficacious dose, consistent with safety and efficacy.

Labels of lozenges containing a local anaesthetic agent should include a label warning statement such as:

- Do not take hot food or drink soon after using this product because it may burn your mouth.

#### Antimicrobial lozenges

See [Sore throat treatments – antimicrobial](#)
**Metered dose inhalers**

**Spacer devices**

A statement consistent with the following should be included in the Product Information for metered dose inhalers used in the treatment of respiratory disorders such as asthma and chronic obstructive airways disease:

*Many patients, including virtually all children, will benefit from the consistent use of a spacer device with their metered dose inhaler (MDI or ‘puffer’), particularly those with poor inhaler technique. Use of a spacer will also decrease the amount of drug deposited in the mouth and back of the throat, and therefore reduce the incidence of local side effects such as mouth and throat irritation.*

*In those people using a spacer, a change in formulation of the drug used, or a change in the make of spacer may be associated with alterations in the amount of drug delivered to the lungs. The clinical significance of these alterations is uncertain. However, in these situations, the person should be monitored for any loss of asthma control.*

*If using a spacer, the patient should be instructed to breathe in and out several times after each release into the spacer. Any delay should be kept to a minimum.*

*Because of electrostatic charge, leading to adherence of drug particles to the walls of the spacer, spacers should be washed in warm water with kitchen detergent and left to drain dry (without rinsing) before initial use and at least monthly thereafter. A cloth should not be used to dry the spacer, as this can produce more static electricity.*

The Product Information should also include information on compatible spacers and a recommendation that patients be directed to read the instructions that come with the spacer.

Consistent advice should also be included in the labelling and/or Consumer Medicine Information.

**Mouth ulcer, relief**

Product labels should contain a statement such as:

- *If symptoms persist, seek medical or dental advice.*

Where an antiseptic is included, the efficacy of the antiseptic must be justified.

**Mouthwashes, antiseptic**

Claims of antiseptic activity must be accompanied by evidence of efficacy. Any claims relating to the duration of action will require justification.

**Napkin rash**

Local anaesthetics and boric acid are not acceptable in any form for the treatment of napkin rash.

**Nonoxinol 9**

*Guideline amended 13 February 2004*

Before any products containing nonoxinol 9 are registered as anti-viral agents, in vivo scientific evidence must be provided.

It is considered that nonoxinol 9 has spermicidal activity provided it is in an appropriate delivery system.
The labelling of all vaginal contraceptive products containing nonoxinol 9 should include advice consistent with the following: “This product does not protect against the AIDS virus (HIV) or other sexually transmitted diseases (STDs)”. Package inserts (or carton labels if there is no package insert) should include the following warnings:

- “For vaginal use only”;
- “This product should not be used rectally”;
- “Sexually transmitted diseases (STDs) alert: This product does not protect against the AIDS virus (HIV) or other sexually transmitted diseases (STDs)”;
- “Ask a doctor before use if you have a new sex partner, multiple sex partners, or unprotected sex. Frequent use (more than once a day) of this product may increase vaginal irritation, which may increase the risk of becoming infected with the AIDS virus (HIV) or other STDs from infected partners. Ask a doctor or other health professional for your best birth control method.”; and
- “Stop use and ask a doctor if you or your partner get burning, itching, a rash, or other irritation of the vagina or penis”.

**Paediatric products**

This guideline applies to medicines that are indicated for use in children (including those that are intended for use in both adults and children). Where label statements are specified, the wording may be varied provided the intent remains the same.

**Use in children under 6 months of age**

Medicines generally should not be administered to children under six months of age except on the advice of a doctor because:

- Serious illnesses in this age group often produce subtle or non-specific symptoms. Sedative, antipyretic and other drugs may confuse the clinical picture, delaying correct diagnosis and treatment; and
- Correct dosage calculation based on weight is essential for many medicines for use in this age group.

Unless otherwise justified, where dosage instructions for children under 6 months of age are included on the labelling, the dosage instructions should advise (at the beginning of the directions for use in this age group) that the product is only to be given in this age group following the advice of a doctor.

In the case of products which are not absorbed and are used for self-limiting conditions (e.g., simethicone ‘wind’ drops), inclusion of a statement such as the following may be considered:

Seek the advice of a pharmacist or doctor before using for the first time in children under 6 months of age.

**Paediatric products containing antihistamines**

The dosage instructions for paediatric products containing antihistamines labelled for use in children under 2 years of age should advise (at the beginning of the directions for use in this age group) that the product is only to be given in this age group following the advice of a health care professional (see also Paediatric cold and flu products below).
Where the product is indicated for sedation in children up to the age of 12 years, the label should also advise (at the beginning of the directions for use in this age group) that the product is only to be given in this age group following the advice of a health care professional.

The labels of paediatric products containing promethazine should advise (at the beginning of the directions for use) that they should not be used in children under 12 months of age and that the advice of a doctor should be sought before administering the product to children from 12 to 24 months of age. A dose for children in the 12 to 24 month age group need not be included on the label where the product has a TGA approved published Product Information (PI) that the doctor can refer to in determining the correct dose. Where there is no PI and no dose on the label, the label must include a statement such as “Not recommended for use in children under 2 years”.

**Paediatric products containing cough suppressants**

Products containing cough suppressants should not be used in children under 12 months of age. The dosage instructions of these products should include a statement to the effect of “Do not use in children under 12 months of age”.

Products containing cough suppressants for use in children between 12 months and 2 years of age should include a direction (at the beginning of the directions for use in this age group) that the product is only to be given in this age group on the advice of a doctor. A dose for children in this age group need not be included on the label where the product has a TGA approved published Product Information (PI) that the doctor can refer to in determining the correct dose. Where there is no PI and no dose on the label, the label must include a statement such as “Not recommended for use in children under 2 years”.

**Paediatric cold and flu products**

Paediatric products for the treatment of symptoms of colds and flu for use in children under 2 years should advise (at the beginning of the directions for use) that the product is only to be used in children under 6 months of age on the advice of a doctor and only in children aged 6 months to 2 years on the advice of a health care professional.

A dose for children under 6 months of age need not be included on the label where the product has a TGA approved published Product Information (PI) that the doctor can refer to in determining the correct dose. Where there is no PI and no dose on the label, the label must include a statement such as “Not recommended for use in children under 6 months”.
Paediatric products – summary of label requirements for advice

<table>
<thead>
<tr>
<th>Category</th>
<th>Label Statement</th>
<th>Under 6 months</th>
<th>6 to 24 months</th>
<th>2 to 11 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medicines generally</td>
<td>Doctor's advice</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Antihistamines not for sedation</td>
<td>Doctor's advice</td>
<td>Health care</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Antihistamines for sedation</td>
<td>Doctor's advice</td>
<td>Health care</td>
<td>Health care</td>
<td>---</td>
</tr>
<tr>
<td>Promethazine</td>
<td>Not to be used</td>
<td>Not to be used</td>
<td>---</td>
<td>---</td>
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<tr>
<td>Cough suppressants</td>
<td>Not to be used</td>
<td>Not to be used</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Cold and flu products</td>
<td>Doctor's advice</td>
<td>Health care</td>
<td>---</td>
<td>---</td>
</tr>
</tbody>
</table>

Where there is a problem in fitting the required text on the label, sponsors are advised to discuss options with the OTC Medicines Section.

See also [Chest rubs](#), [Corn treatments](#), [Diarrhoea treatments](#), [Family packs](#), [Fluoride-containing preparations](#), [Ibuprofen](#), [Lozenges](#) and [Paracetamol](#)
Paracetamol

Indications
Sponsors may use any or all of the representative indications set out below (or similar) as appropriate to a particular product without the need to supply supporting efficacy data:

For the temporary relief of pain (and discomfort) associated with: headache, migraine headache, toothache, dental procedures, backache, muscular aches, arthritis, rheumatics, menstruation/period pain, sore throat, osteoarthritis and symptoms of cold and flu. Reduces fever and/or the discomfort associated with fever.

For paediatric formulations, teething, earache and immunisation may be added to any of the above, as appropriate to the age group.

Sponsors may propose other indications but should contact the OTC Medicines Evaluation Section for advice on whether data will be required to support the safety and efficacy of the product for those indications.

As fever is a normal and beneficial response to infection, no elaboration to the words “reduces fever” will be accepted except with regard to the duration of treatment and with regard to the relief of discomfort associated with fever.

Mandatory warning statements
Warning statements should be included on the label as specified in the Standard for the uniform scheduling of drugs and poisons (SUSDP).

Dose

Adult dosage recommendations (adults and children 12 years and over)
500 to 1000 mg every four to six hours as necessary. Dosage should not exceed 4 g (expressed on the label as number of units, eg. tablets) in 24 hours.

Paediatric dosage recommendations (1 month to 12 years)
The dose should be based on 15 mg/kg, with the understanding that dosing with solid dose products for this age group is less flexible than with liquid products.

The total daily dose should not exceed 60 mg/kg without medical advice.

Doses should be given every four to six hours as required with not more than four doses in 24 hours. The medicine should not be administered for more than 48 hours without seeking medical advice. Administration to children under one month is not recommended. Statements to this effect must appear on labels of the primary pack and the immediate container.

<table>
<thead>
<tr>
<th>Age</th>
<th>Average body weight (kg)</th>
<th>Single dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 - 3 months</td>
<td>4 – 6</td>
<td>60 - 90</td>
</tr>
<tr>
<td>3 - 6 months</td>
<td>6 – 8</td>
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<tr>
<td>3 - 4 years</td>
<td>14 – 16</td>
<td>210 - 240</td>
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</table>

<table>
<thead>
<tr>
<th>Age</th>
<th>Average body weight (kg)</th>
<th>Single dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 - 5 years</td>
<td>16 – 18</td>
<td>240 - 270</td>
</tr>
<tr>
<td>5 - 6 years</td>
<td>18 – 20</td>
<td>270 - 300</td>
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<td>6 - 7 years</td>
<td>20 – 22</td>
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<td>7 - 8 years</td>
<td>22 – 25</td>
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<td>25 – 28</td>
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<td>420 - 480</td>
</tr>
<tr>
<td>10 - 11 years</td>
<td>32 – 36</td>
<td>480 - 540</td>
</tr>
<tr>
<td>11 - 12 years</td>
<td>36 – 41</td>
<td>540 - 615</td>
</tr>
</tbody>
</table>

Doses must be expressed in whole numbers and should be presented with age, weight and mL unless otherwise justified.

The recommended dose should be able to be measured using commonly available metric measuring devices. There may be instances where the dose needs to be slightly different than the recommended milligram dose given above, having regard to the paracetamol concentration of the product. Sponsors intending to supply measuring devices with the product should consult Australian Standard AS 2224.2 - 1986.

Calibrations on measuring devices should be in metric units and correspond with the doses shown on the label where possible to minimise the need for calculation and guesswork.

**Product Strength and pack size**

Sponsors may supply any or all of the following strengths of paracetamol liquid without the need for justification: 24 mg/mL, 48 mg/mL, 50 mg/mL and 100 mg/mL. Deviation from these strengths requires justification.

While not prohibited, the introduction of pack sizes larger than 200 mL will require justification.

**Combination products**

Products containing more than one active ingredient which are similar to existing registered products will usually not require efficacy or safety data, provided they comply with the guideline on Multi-component products (in Chapter 4B, Formulation). Where new combinations are proposed (ie. combinations and/or strengths that are not included in the Australian Register of Therapeutic Goods for supply in Australia), the safety and efficacy of the combination will need to be justified.

Where paracetamol is used in combination with other active ingredients, the indications listed above for paracetamol may be appropriate for the combination product subject to compliance with the guideline on multi-component products.

Due to the lack of flexibility when dosing with combination products and because the majority of patients require more than 500 mg of paracetamol for effective analgesia, products should be formulated so that doses of other ingredients are at safe and effective levels when at least 600 mg of paracetamol is taken.

**Differentiation of strengths**

Sponsors of liquid paracetamol products are requested to give close consideration to labelling and presentation with a view to minimising the possibility of parents or carers accidentally administering the wrong strength to the child.

See also Paediatric products
Phenylalanine

See Aspartame

Phenylpropanolamine

See Decongestant products, oral

Povidone-iodine/iodine – dermal

Products for dermal use should contain a statement such as:

- If skin irritation or rash occurs, discontinue use immediately.

Pseudoephedrine

See Decongestant products, oral

Rubefacients

The following statement of indications (or similar) will generally be accepted for rubefacient products:

- For the temporary relief of the pain of rheumatism, arthritis, fibrositis, lumbago, muscular aches and strains.

Lumbago is defined as backache in the lumbar or lumbosacral regions.

Sciatica, neuritis, bruising, swelling and cramps will not be approved as indications for rubefacient products.

Product labels should contain a statement such as:

- This product should not be used in conjunction with heat pads.

This is due to the possibility of myolysis when rubefacients are used in conjunction with heat pads (reference details to be included).

Sodium bicarbonate

The use of sodium bicarbonate and other alkaline bicarbonates as antacids is undesirable. While effervescent preparations containing sodium bicarbonate will be considered for registration, products containing high levels of sodium and bicarbonate are discouraged.

See also Sodium content

Sodium content

Guideline amended 24 September 2003

Products for oral administration containing more than 120 mg of sodium per maximum recommended daily dose should include a statement such as the following on the label:

- This preparation contains XX mg (YY mmol) per dose of sodium which should be taken into account by those on a low sodium diet.
Where the recommended adult dosage provides 23 mg (1 mmol) or more of sodium per dose, the sodium content of the formulation should be justified.

**Sore throat treatments – antimicrobial**

Antimicrobial agents have traditionally been included in sore throat treatments (gargles, sprays and lozenges) on the assumption that short-term topical inhibition of the bacteria, viruses or fungi implicated in the cause of sore throats might shorten the duration of the infection. Unless and until this assumption is shown to be correct, sponsors of sore throat treatments making antimicrobial claims will be required to substantiate these claims with clinical evidence of efficacy for the proposed formulation.

Alternatively, if the sponsor wishes to make unsubstantiated antimicrobial, antibacterial or antiseptic claims, the label should contain a statement to alert consumers that they should not expect the presence of the antibacterial agent to reduce the severity or duration of a sore throat, such as:

- The presence of the antibacterial/antimicrobial/antiseptic agent in this product has not been shown to have a beneficial effect on the severity or duration of a sore throat.

The proposed indications for such products should be restricted to symptomatic relief of sore throat.

See also [Lozenges](#)

**Sympathomimetic amines**

See [Decongestant products, oral](#)

**Tryptophan**

Products containing tryptophan will not be approved for indications such as insomnia, anxiety or other depressive illness in the absence of scientific evidence. Reports of interactions with antidepressants resulting in adverse effects are further reason for caution.

**Urinary alkalinisers**

Products intended to produce alkalinisation of the urine should include label warning statement such as:

- Consult a doctor if pain or irritation persists for more than 48 hours or if you notice blood in your urine;

- Do not take this medicine for more than five days unless advised to do so by a doctor;

- Do not give this medicine to children under 12 years of age unless advised to do so by a doctor; and

- Check with a doctor or pharmacist before using this medicine if you are taking other medicines or if you have kidney problems, heart problems or high blood pressure.
Vaginal itch, topical preparations

Products containing local anaesthetics will not be approved for the topical treatment or relief of vaginal itch.

Other products for symptomatic relief of vaginal itch should include a statement such as:

- For temporary relief of symptoms only. If symptoms persist, seek medical advice.

Wart treatments

The following statements (or similar) should be included on labels:

- Do not use if you have diabetes or impaired circulation.

- Use only on common warts. Do not use on moles, birthmarks or unusual skin growths. Do not treat warts over large areas at one time.
10. Sunscreens

Chapter added 24 September 2003

Introduction

Australia has the highest rate of melanoma in the world. Many Australians use sunscreen every day of their lives, sometimes over large areas of their body surface. It is important therefore that sunscreens used in Australia are safe and effective and of good quality.

This chapter describes the regulatory requirements for sunscreens and their ingredients in Australia. It replaces all information on sunscreens contained in the TGA publication, Listing drug products in the Australian Register of Therapeutic Goods for supply in Australia: Guidelines for applicants.

Medicine or cosmetic?

Most sunscreens are regulated as medicines under the Therapeutic Goods Act 1989. Some products that contain an ingredient with sunscreens properties are regulated as cosmetics rather than as medicines where the primary purpose is not sunscreens. These cosmetic products are referred to as ‘excluded’ sunscreens and are not regulated under therapeutic goods legislation.

A table at the end of this chapter (Summary of sunscreen regulation) summarises the current regulation of the various categories of sunscreens. This information is based on the Therapeutic Goods (Excluded Goods) Order No. 1 of 1998, Therapeutic Goods (Excluded Goods) Order No. 2 of 1998 and the Therapeutic Goods Regulations 1990.

The labelling of cosmetics is regulated by the Australian Competition and Consumer Commission (ACCC). The safety of ingredients used in cosmetics is regulated by the National Industrial Chemicals Notification & Assessment Scheme (NICNAS).

Regulatory requirements for sunscreens

Most sunscreens currently defined as medicines can be 'listed', some are exempt from registration or listing and some must be 'registered' in the Australian Register of Therapeutic Goods (ARTG). General information on listing and registration is available on the TGA website.

Exempt sunscreens

These sunscreens do not require registration or listing in the Australian Register of Therapeutic Goods (ARTG) but are treated as medicines in all other respects. They must comply with all relevant parts of the legislation, for example:

- The Labelling Order (Therapeutic Goods Order No. 69);
- The Therapeutic Goods Advertising Code.

3 http://www.accc.gov.au/content/index.phtml/itemId/142
Sunscreen products are ‘exempt’ if:

- The claimed SPF (established by testing according to AS/NZS 2604:1998) is 3 or less; and
- The label claims comply with AS/NZS 2604:1998; and
- The product does not contain ingredients of human origin or from cattle, sheep, goats or mule deer that are derived from body parts listed in the Regulations (e.g. adrenal glands, brain).

Exempt products can only contain active ingredients that are included in the list of Sunscreening agents permitted as active ingredients in listed products within the maximum concentrations stated in the list.


**Listing of sunscreens**

The majority of sunscreen products require listing in the ARTG. Products are eligible for listing where:

- The claimed SPF has been tested according to AS/NZS 2604:1998 and is 4 or greater; and
- The product does not make a ‘prohibited’ or ‘restricted’ representation as defined in Appendix 6 to the Therapeutic Goods Advertising Code (note that “prevention of skin cancer through the use of sunscreens” is not a ‘prohibited representation’ for some sunscreens); and

Sunscreen products that are otherwise exempt will require listing where the product does contain ingredients of human origin or from cattle, sheep, goats or mule deer that are derived from parts listed in the *Therapeutic Goods Regulations 1990* (e.g. adrenal glands, brain).

Applications for listing of sunscreen products that contain material of human or animal origin as above must include a pre-clearance certificate issued by the TGA Laboratories Branch (TGAL).

Listed sunscreen products can only contain active ingredients that are included in the list of Sunscreening agents permitted as active ingredients in listed products within the maximum concentrations stated in the list.

Sponsors should consider the impact of excipients on the sensitivity of the skin to sunlight and should ensure the finished product is safe for its intended purpose.

Sunscreen products that make claims other than sunscreening (e.g. ‘antioxidant’ claims or claims relating to reduction of UV induced immune suppression) and / or contain active ingredients that are not included in the list of Sunscreening agents permitted as active ingredients in listed products are not ‘sunscreen preparations’ and must be registered as an OTC medicine rather than listed in the ARTG (see below for details of registration).

All other sunscreen products (i.e. those that are neither exempt nor listable) must be registered in the ARTG.

Information on the listing process can be found on the TGA website.


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Registration of sunscreens

‘Registration’ is the default category for sunscreens that are not ‘exempt’ or ‘listable’. These products are evaluated by the TGA for quality, safety and efficacy under the provisions of Section 25 of the Therapeutic Goods Act 1989.

- Products that are to be included in the Schedule of Pharmaceutical Benefits;
- Products that contain a sunscreen active ingredient that is not included in the list of Sunscreening agents permitted as active ingredients in listed products;
- Products that make therapeutic claims other than sunscreening;
- Products that are not otherwise ‘exempt’ or ‘listable’.

Labelling of sunscreens

The labelling of sunscreen products must comply with:

- The Labelling Order (Therapeutic Goods Order No. 69)\(^\text{11}\);
- The Therapeutic Goods Advertising Code\(^\text{12}\);
- Australia/New Zealand Standard AS/NZS 2604:1998\(^\text{13}\).

Note that AS/NZS 2604:1998 has particular requirements for the labelling of sunscreens:

- Specifications for the declaration of the SPF;
- Limitations on “broad spectrum” claims;
- Limitations on the use of “water resistant” claims.

The following claims are permitted for broad spectrum sunscreen preparations with a sun protection factor of ‘30 plus’:

- may assist in preventing some skin cancers;
- may reduce the risk of some skin cancers;

provided that the product label highlights the need for avoidance of prolonged exposure to the sun and the importance of wearing protective clothing, hats and eyewear. Reference: Gazette notice: Advertising sunscreens, 13 September 2002\(^\text{14}\).

A broad-spectrum sunscreens preparation may make the claim “can aid in the prevention of premature skin ageing” or words to that effect.

[^“30+” deleted after “broad spectrum” 13 February 2004]

The labels of sunscreen products should include statements to the effect of the following:

- Advise consumers to apply generous amounts of sunscreen over all exposed areas 15 to 20 minutes before sun exposure, and again after swimming or towelling.
- Highlight the need for avoidance of prolonged exposure to the sun and the importance of wearing protective clothing, hats and eyewear.

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Advise consumers to keep the product out of the eyes.

The first and second requirements above do not apply to secondary sunscreens (those sunscreen products that are represented on the label as protecting the skin from harmful effects of the sun’s rays while fulfilling another primary function). None of the above labelling requirements apply to lip preparations.

**Stability testing of sunscreens**

Guidelines for the stability testing of sunscreen products have been compiled by industry peak bodies and agreed by the TGA. Sponsors of all sunscreen products are expected to have performed stability testing on each product to at least the standard set out in these guidelines. The claimed shelf life and storage conditions for each product should be derived from the results of the stability testing on that product.

The stability testing guidelines for listed sunscreens can be found on the Australian Self Medication Industry (ASMI) website\(^\text{15}\). The stability testing guidelines for registered sunscreens can be found in Chapter 4E, *Stability testing*.

**Microbial content and preservative efficacy of sunscreens**

Sunscreen products in all categories (exempt, listed or registered) are expected to comply with the TGAL guidelines for microbiological testing for ‘products for topical application’ in Chapter 4F, *Microbiological testing*, and to comply with the preservative efficacy test in the current edition of the *British Pharmacopoeia*.

**Manufacturers of sunscreens**

Manufacturers of listed or registered sunscreens must be licensed or approved by the TGA. Information on licensing/approval is available on the TGA website\(^\text{16}\).

Manufacturers of sunscreens are required to comply with the Australian Code of GMP for Therapeutic Goods – Sunscreen Products\(^\text{17}\).

**Sunscreening agents permitted as active ingredients in listed or exempt products**

The only active ingredients permitted in exempt or listed sunscreens are those included in the table of *Sunscreening agents permitted as active ingredients in listed or exempt products*, within the maximum concentrations stated in the list. This list replaces the list included in the TGA publication, *Listing drug products in the Australian Register of Therapeutic Goods for supply in Australia: Guidelines for applicants*\(^\text{18}\) (pp 35 – 37).

Sponsors wanting to market a product containing an active ingredient not on the list must submit data to establish the safety of the ingredient under its proposed conditions of use (see below).

**New active ingredients in sunscreens**

Guidelines for the approval of new substances are given in Chapter 6B, *New substances*. This section (below) describes the specific requirements that apply to new sunscreen active ingredients and should be read in conjunction with Chapter 6B.


\(^{16}\) http://www.tga.gov.au/industry/manuf.htm

\(^{17}\) http://www.tga.gov.au/industry/manuf-sunscreens-cgmp.htm

### Data requirements

The table (below) gives specific references to the relevant guidelines for the types of data that are usually required for a new sunscreen active ingredient. All EU guidelines referenced below have been adopted by the TGA.

The intention in specifying these guidelines is not to impose them as absolute requirements but to assist sponsors in assessing the type and depth of information needed to support an application. If a particular guideline is not applicable or other data are available that adequately address the same criteria, alternative approaches based on adequate scientific justification will be considered.

<table>
<thead>
<tr>
<th>Type of data</th>
<th>European guidelines reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>- UV absorption spectra</td>
<td></td>
</tr>
<tr>
<td>- skin irritation</td>
<td></td>
</tr>
<tr>
<td>- phototoxicity</td>
<td></td>
</tr>
<tr>
<td>- eye irritation</td>
<td></td>
</tr>
<tr>
<td>- skin sensitisation</td>
<td></td>
</tr>
<tr>
<td>- photosensitisation</td>
<td></td>
</tr>
<tr>
<td>- ADME studies</td>
<td></td>
</tr>
<tr>
<td>(oral &amp; dermal) – 3 to 6 months data</td>
<td>See also: Note for guidance on duration of chronic toxicity testing in animals (rodent and non-rodent toxicity testing) (CPMP/SWP/300/95)  <a href="http://www.tga.gov.au/docs/pdf/euguide/ich/030095entga.pdf">http://www.tga.gov.au/docs/pdf/euguide/ich/030095entga.pdf</a></td>
</tr>
</tbody>
</table>

* a. ADME = Absorption, Distribution, Metabolism, Excretion

b. Genotoxicity and photomutagenicity testing are specific to the risks associated with the active ingredient.
Type of data | European guidelines reference
--- | ---

Note for guidance on genotoxicity: A standard battery for genotoxicity testing of pharmaceuticals (CPMP/ICH/174/95)

Reproductive toxicity c, e | Detection of toxicity to reproduction for medicinal products including toxicity to male fertility (pp 25-44 of Rules 1998 (3B) – 3BS4a)

Carcinogenicity d | Carcinogenic potential (pp 63-67 of Rules 1998 (3B) – 3BS7a)

photocarcinogenicity | Interaction potential
Since sunscreen formulations usually contain more than one active ingredient, data on the potential for interaction of the new substance with other UV filters will usually need to be provided.

a. An in vivo determination of dermal and oral absorption is needed to establish systemic exposure via both routes and to enable interpretation of the toxicity studies.
b. Genotoxicity testing in bacterial and mammalian cell lines, photomutagenicity test in bacteria, photomutagenicity in a chromosomal aberration test and an in vivo chromosome aberration assay.
c. For assessment of developmental and fertility effects.
d. In vivo carcinogenicity and photocarcinogenicity bioassay or a justification for not providing these studies (see below).
e. Endocrine disruption potential needs to be addressed. This could be examined during the repeat-dose toxicity and/or reproductive toxicity studies.

Relevant human studies are acceptable in the assessment of potential skin irritation and sensitisation using the repeat insult patch test or other relevant validated tests.

**Justification for not providing particular studies**

In circumstances where particular tests specified in the table above are not feasible or appropriate, sponsors should submit a justification, based on sound scientific argument, for not including these tests in the dossier.

In the case of in vivo carcinogenicity bioassays, a justification for not including long-term studies could be based around issues such as:

- the expected pattern of use (identify possible low exposure);
- results of mutagenicity studies;
- lack of similarity to other molecules with known carcinogenic activity;
- low persistence in the skin;
- low in vivo absorption;
- lack of photosensitisation or phototoxic potential;
- proven photostability;
• lack of possible adverse effects on the skin (change to epidermis/dermis);
• length of submitted repeat dose toxicity studies.

**Related studies**

Other studies that are not currently referenced in EC guidelines may be useful in supporting particular applications. Reference to these studies is included only as a guide. They will not be relevant in all cases, nor should they be seen as a complete list of relevant studies.

The following studies may be useful in providing information on the potential of a substance to cause tumours in people:

- Studies using a transgenic mouse model to test exposure to the substance (the transgenic mouse is heterozygous for the p53 suppressor gene and tumours develop in a relatively short time frame (6 months) in this strain of mouse);\(^{19}\);
- *In vitro* human dermal cell cultures exposed to the substance;\(^{20}\);
- *In vitro* human dermal tumour cell cultures exposed to the substance.

The following references may be useful in justifying the use of ingredients with a potential for skin corrosion/irritation:

- Non-animal testing strategies for assessment of the skin corrosion and skin irritation potential of ingredients and finished products; M K Robinson *et al*; *Food and Chemical Toxicology*, 40(5), pp 573-592, 2002.

**Chemistry requirements**

In addition to the requirements stated in Chapter 4B, *Formulation*, sponsors should provide data to establish the UV absorption range of the substance together with data addressing the potential for physical interaction with other commonly used sunscreens agents.

**New excipients in sunscreens**

Where a sunscreen contains an excipient ingredient which is not in any product currently included in the Australian Register of Therapeutic Goods (ARTG) for supply in Australia, the excipient must be cleared for use by the TGA.

The following information is required:

1. Identification of the excipient as a substance included in the CTFA International Cosmetic Ingredient Dictionary (the page number and reference should be quoted); and
2. Assurance that it does not appear in Annex II to the EEC Directive 76/768 List of substances which must not form part of the composition of cosmetic products; and
3. Assurance that the excipient has been approved by the appropriate regulatory agency in Sweden, Canada, USA, UK or The Netherlands; or (less desirably)
4. Assurance by the applicant that there have been market-place sales of comparable products containing the excipient in one of those five countries for at least two years; and

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\(^{19}\) Reference: *Novel systems for the study of human diseases*; OECD Proceedings; OECD Online Bookshop Code 931998021P1 (Page 400)

\(^{20}\) Methodology for these studies can be obtained from the scientific literature
5. Acute oral toxicity: LD50 – animal or alternative method; and

6. Irritation study – skin; animal or alternative method; and

7. Sensitisation study – skin; animal or alternative method.

The following additional studies may be requested in individual cases where concerns become evident at the time of evaluation.

1. Eye irritation study; and

2. *In vitro* mutagenicity (Ames) test; and

3. *In vitro* percutaneous absorption test.

All of the above information can be submitted prior to listing together with the *New substance application form* 21 (available from the TGA website). If the substance is cleared it will be given an ‘Australian Approved Name’ (AAN) and will thereafter be able to be used in other topical non-prescription medicines (subject to any conditions or limitations) without the need for further evaluation. The sponsor will be advised of the AAN and will then be able to submit an application to list/register the sunscreen product.

Alternative sources of data on the safety of the excipient will be considered. For instance, if the excipient has been cleared by NICNAS or by the US Cosmetic Ingredient Review (CIR) group the review document may be sufficient in itself. Copies of CIR reviews are available on the Internet 22. Copies of NICNAS reviews may be available from the supplier of the excipient.

Alternatively, the information in the first four points above can be submitted as part of a 'Listing' application for a sunscreen together with an assurance that the data specified in points 5 to 7 will be provided to the TGA within 6 months of the date of listing of the product. The new excipient will be given a ‘provisional AAN’ (known as a ‘PRV’) and the product listed with a condition that the data must be provided within 6 months of listing. Failure to submit the specified data within this time may result in cancellation of the product from the ARTG and recall.

The data will be evaluated by the TGA and, if cleared, the excipient will be given an AAN and will thereafter be able to be used in other topical non-prescription medicines (subject to any conditions or limitations) without the need for further evaluation. If there are concerns about the safety of the excipient or if the data provided by the sponsor are incomplete or otherwise unacceptable, the product may be cancelled from the register and/or recalled.

Fees will apply to the evaluation of the data and the listing of the product as specified in the *Summary of fees and charges* 23.

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## Summary of sunscreen regulation

<table>
<thead>
<tr>
<th>Product category</th>
<th>Sub-category</th>
<th>Currently regulated by TGA as:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lovable sunscreens</td>
<td>Sunscreens or moisturisers making SPF claims (or equivalent) where SPF is 4 or greater and claims are limited to sunscreening. Sunscreens that are otherwise exempt but contain certain ingredients of animal origin (see note below).</td>
<td>Listing in the ARTG.</td>
</tr>
<tr>
<td>Registrable sunscreens</td>
<td>Sunscreens that are included in the Schedule of Pharmaceutical Benefits. Sunscreens that make therapeutic claims other than sunscreening.</td>
<td>Registration in the ARTG.</td>
</tr>
<tr>
<td>Exempt sunscreens</td>
<td>Sunscreens or moisturisers making SPF claims (or equivalent) where SPF is 3 or less, claims are limited to sunscreens and the product does not contain certain ingredients of animal origin (see note below).</td>
<td>Exempt from listing or registration in ARTG, exempt from being made by a licensed manufacturer. Note: these sunscreens are still regulated as ‘medicines’ and must comply with the Labelling Order.</td>
</tr>
<tr>
<td>Excluded sunscreens</td>
<td>Tinted, unmedicated lip preparations (includes lipstick) without therapeutic claims (other than sunscreening) with or without SPF or equivalent declared on label. Other cosmetics (including moisturisers) without therapeutic claims (other than sunscreening) and without SPF claims or equivalent on the label.</td>
<td>Regulated by NICNAS / ACCC as a cosmetic</td>
</tr>
</tbody>
</table>

Note: The preceding table is a summary of legislative provisions. For complete details the following documents should be referred to:

- *Therapeutic Goods Regulations 1990*

Sunscreening agents permitted as active ingredients in listed products

Table corrected 18 August 2006

<table>
<thead>
<tr>
<th>Australian Approved Name (AAN)</th>
<th>EC &amp; USA/FDA name</th>
<th>Synonyms/abbreviations/trade names</th>
<th>Maximum concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminobenzoic acid</td>
<td>4-Aminobenzoic acid</td>
<td></td>
<td>15%</td>
</tr>
<tr>
<td>Isoamyl methoxycinnamate</td>
<td>Isopentenyl-4-methoxycinnamate (Isoamyl 4-methoxycinnamate)</td>
<td></td>
<td>10%</td>
</tr>
<tr>
<td><strong>Benzophenone</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benzophenone-2</td>
<td>Benzophenone-2</td>
<td>Phenylketone</td>
<td>To be determined</td>
</tr>
<tr>
<td>Butyl methoxy dibenzoylmethane</td>
<td>1-(4 tert butylphenyl)-3(4-methoxyphenyl)propane-1,3-dione</td>
<td>Avobenzone, BMDM, 4-tert-butyl-4-methoxy dibenzoylmethane</td>
<td>5%</td>
</tr>
<tr>
<td>Cinoxate</td>
<td>Cinoxate</td>
<td></td>
<td>6%</td>
</tr>
<tr>
<td>Dioxybenzone</td>
<td>Dioxybenzone</td>
<td>Benzophenone 8</td>
<td>3%</td>
</tr>
<tr>
<td>Ethoxylated ethyl 4-amino benzoic acid</td>
<td></td>
<td>Ethoxylated ethyl 4-amino benzoic acid</td>
<td>10%</td>
</tr>
<tr>
<td>Padimate O</td>
<td>2-Ethylhexyl 4-dimethylaminobenzoate</td>
<td>Octyl dimethyl PABA</td>
<td>8%</td>
</tr>
<tr>
<td>Octyl methoxycinnamate</td>
<td>Octyl methoxycinnamate</td>
<td>Ethylhexyl Methoxycinnamate</td>
<td>10%</td>
</tr>
<tr>
<td>Octyl salicylate</td>
<td>2-Ethylhexyl Salicylate</td>
<td></td>
<td>5%</td>
</tr>
<tr>
<td>Homosalate</td>
<td>Homosalate</td>
<td>Homomethyl salicylate</td>
<td>15%</td>
</tr>
<tr>
<td><strong>Isopropylbenzyl salicylate</strong></td>
<td>4-Isopropylbenzyl Salicylate</td>
<td>To be determined</td>
<td></td>
</tr>
<tr>
<td>Menthyl anthranilate</td>
<td>Menthyl Anthranilate</td>
<td>Methyl 2-aminobenzoate</td>
<td>5%</td>
</tr>
<tr>
<td>4 Methylbenzylidene camphor</td>
<td>3-(4-Methylbenzylidene)-d-1 camphor</td>
<td></td>
<td>4%</td>
</tr>
<tr>
<td>Octocrylene</td>
<td>2-cyano-3,3-diphenyl acrylic acid, 2-ethyl hexyl ester</td>
<td>2-Ethylhexyl-2-cyano-3,3 diphenylacrylate</td>
<td>10%</td>
</tr>
</tbody>
</table>

This is a historic document and is provided for historical reference only. Please refer to the ARGOM for the most current information.
<table>
<thead>
<tr>
<th>Australian Approved Name (AAN)</th>
<th>EC &amp; USA/FDA name</th>
<th>Synonyms/abbreviations/trade names</th>
<th>Maximum concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Octyl triazone</td>
<td>2,4,6-Trianalino-(p-Carbo-2'-ethylhexyl-1’oxy)1,3,5-Triazine alpha-(2-Oxoborn-3'-ylidene)toluene-4-sulphonic acid and its salts</td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td>Oxybenzone</td>
<td>Oxybenzone</td>
<td>Benzophene 3</td>
<td>10%</td>
</tr>
<tr>
<td>Phenylbenzimidazole sulfonic acid</td>
<td>2-Phenylbenzimidazole-5-sulfonic acid and its potassium, sodium and triethanolamine salts N,N,N-Trimethyl-4-(oxoborn-3'-ylidenemethyl) anilinium methyl sulphate</td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td>Sulisobenzone 2</td>
<td>Sulisobenzone sodium</td>
<td>Benzophene 4</td>
<td>10%</td>
</tr>
<tr>
<td>Ecamsule</td>
<td>Terephthalyldiene dicamphor sulfonic acid</td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td>Titanium dioxide</td>
<td>Titanium dioxide</td>
<td>25%</td>
<td></td>
</tr>
<tr>
<td>Triethanolamine salicylate</td>
<td>Trolamine salicylate</td>
<td>12%</td>
<td></td>
</tr>
<tr>
<td>Zinc oxide 1</td>
<td>Zinc oxide</td>
<td>No limit 1</td>
<td></td>
</tr>
<tr>
<td>Bemotrizinol 3</td>
<td>Bemotrizinol</td>
<td>Tinosorb S</td>
<td>10%</td>
</tr>
<tr>
<td>Methylene bis-benzotriazolyl tetramethylbutyl phenol 4</td>
<td>2,2’-Methylene-bis-6-(2H-benzotriazol-2yl)-4-(tetramethyl-butyl)-1,1,3,3-phenol</td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td>Drometrizole trisiloxane 5</td>
<td>phenol,2-(2H-benzotriazol-2-yl)-4-methyl-6[2-methyl-3-{1,3,3-tetramethyl-1-[(trimethylsilyl)oxy]disiloxany]propyl</td>
<td>Mexoryl XL</td>
<td>15%</td>
</tr>
<tr>
<td>Disodium phenyl dibenzimidazole tetrasulphonate 6</td>
<td>2,2’-(1,4-Phenylen) bis-(1-H-benzimidazole-4,6-disulfonic acid, monosodium salt)</td>
<td>Bisimidazylate, Neoheliopan AP</td>
<td>10%</td>
</tr>
<tr>
<td>Polysilicone-157</td>
<td>Dimethicondiethylbenzalmonate</td>
<td>Parsol SLX</td>
<td>10%</td>
</tr>
</tbody>
</table>

1. Maximum concentration for zinc oxide amended 12 December 2003  
2. ’Benzophene-4’ deleted from column 1 and ’Sulisobenzone’ moved from column 2 to column 1, 25 June 2004  
3. ’Bemotrizinol’ added 22 November 2004
4. 'Methylene bis-benzotriazolyl tetramethylbutyl phenol' added, 22 November 2004
5. 'Drometrizole trisiloxane' added, 6 December 2004
6. 'Disodium phenyl dibenzimidazole tetrasulfonate' added, 31 August 2005
7. 'Polysilicone' added, 18 August 2006

Shading indicates that the sunscreen agent is currently under review – new products containing any of these ingredients will not be listed until the review has been completed.

Note: Sponsors wanting to market a product containing an active ingredient not on this list must submit data to establish the safety of the ingredient under its proposed conditions of use (See New active ingredients in sunscreens).
11. Changes to OTC medicines

Is notification or prior approval required?

Following the inclusion of your product as a registered OTC medicine in the Australian Register of Therapeutic Goods (ARTG), you may wish to change certain details held by the TGA. Influences such as product stability, manufacturer changes and developing marketing strategies may dictate changes to product details which were approved at the time of the product’s inclusion in the ARTG.

It is a condition of registration of your goods that you notify the TGA of any changes in information that may have been relevant to a decision to register the goods.

The Changes table in this Chapter sets out the steps that you must take before proceeding with a change. Note that the Therapeutic Goods Act 1989 provides for penalties where a change is implemented without the approval of the TGA (see subsection 22(3) of the Act).

About this document

While this document gives summary information about the legislation, you are strongly advised to refer to the legislation itself for complete information on the implications for your product. This document refers only to registered OTC medicines. It does not apply to listed medicines, complementary medicines or medicines of the type evaluated by the Drug Safety and Evaluation Branch.

Which form do I fill in?

Applications for variation of an existing product should be made on the Registered medicine variation form (OTC)\(^1\). Applications for registration of a new product should be made on the New medicine registration application form (OTC)\(^2\). These forms are available on the OTC medicines page\(^3\) of the TGA website.

How much will it cost?

All applications directed to the Non-Prescription Medicines Branch, whether requiring notification or prior approval, will attract an application fee. For applications which require approval, a separate evaluation fee is payable. Information on current fees is available on the TGA website\(^4\) or from the TGA Publications Office – Freecall 1800 020 653.

The Therapeutic Goods Regulations provide for the waiver or reduction of evaluation fees under certain circumstances. If the change to your product is such that you feel you are eligible for a waiver or reduction of the evaluation fee you should pay the full fee at the time of application and include a request for waiver/reduction with the application. Reductions or waivers are not granted as a matter of course. Each application is judged on its own merits. If approved, the appropriate


amount will be refunded by the Business Management Unit. Processing delays may result if the correct fees are not paid at the time of application.

Refer to Regulation 45 of the *Therapeutic Goods Regulations* for the criteria applying to the waiver and/or reduction of fees.

**Does the change make the goods ‘separate and distinct’?**

Some changes may render the changed goods *separate and distinct* from the present goods. Section 16 of the Act lists those criteria which make goods *separate and distinct*. Where the *Therapeutic Goods (Groups) Order* (the ‘Groups Order’) applies, the ‘new’ goods, although technically *separate and distinct* from the present goods, may be ‘grouped’ in the same register entry as the existing goods. If the ‘new’ goods are *separate and distinct* and the *Groups Order* does not apply, you will need to submit a new application for registration of the goods.

See [Groups Order](#) for a summary of the provisions of the *Therapeutic Goods (Groups) Order*.

**What else do I need to send?**

For applications that require approval, and for some applications that require notification, you will need to submit further documentation with the variation form. Some supporting documentation requirements are self-evident. If you wish to change details of the label, for example, you will need to send a copy of the present label and a draft copy of the new label, highlighting the changes (note that finished artwork is not necessary at this stage).

In other cases, what is required as supporting documentation may not be so evident. If you have consulted the various references and are still unsure, contact the staff of the OTC Medicines Section.

In some instances, certain assurances about the change will also need to be made before the application can proceed. Where these are required, details are given in the [Changes table](#). Note that it is your responsibility to ensure that the required assurances are given in your application. If they are not given, the change may require prior approval, rather than notification.

**Other aspects of the product (that are not being changed)**

Generally, only the requested change will be reviewed at the time of application. However, some changes naturally impact on other aspects of the product which may require further clarification. If a problem is detected which is unrelated to the requested change it may be followed up as a separate issue but will not generally hold up processing of the application.

Obviously, some flexibility will be necessary, as it may be in the interests of both the TGA and the sponsor to have all outstanding issues resolved before the change is implemented.

Sponsors should be aware that sometimes a proposed change might involve additional consequential changes (eg. removal of a colouring agent may also require change to visual identification). In such cases each of the relevant changes should be specified in the application.

**The same changes for many products?**

If you wish to implement an identical change across a range of similar products, only one application form may need to be completed in certain cases. An example is the notification of a change of the same principal manufacturer (licensed) for a range of registered products.
What if the proposed change is not in the Changes table?

If you cannot find a description of your proposed change in the Changes table, contact the staff of the OTC Medicines Section. The absence of your proposed change does not imply that you may proceed with the change without notifying us or seeking prior approval of the change.

Acknowledgment of application

You will be sent an acknowledgment by the Business Management Unit (BMU) in response to all submissions for changes which require either notification or prior approval. For changes requiring notification, you need not wait until you receive the acknowledgment of your notification before implementing the change.

For changes that require prior approval, a letter of approval, signed by the delegate of the Secretary, is sent. It is important that you do not proceed with this type of change until you receive the approval letter. Should your application be refused, a rejection letter containing details of procedures for review of the decision will be sent.

Groups Order – summary

The ‘Groups Order’ specifies the circumstances in which ‘separate and distinct’ therapeutic goods can be ‘grouped’ in the same ARTG entry (ie. under the same AUST R number).

Section 16 of the Therapeutic Goods Act 1989 sets out the criteria which make goods ‘separate and distinct’. These are:

- a different name; or
- different indications; or
- different directions for use; or
- a different type of container; or
- a different dosage form; or
- a different formulation or composition.

When the Groups Order does not apply, the changed goods must have a separate ARTG entry and bear a separate AUST R number. If this is the case, you should apply for registration of the changed goods as if it were an entirely new product.

The provisions of the Groups Order (as applied to non-prescription drug products) may be summarised as follows:

Name change

Goods may be grouped when the only difference between the new goods and the existing goods is the proprietary name and when the new goods are to replace the existing goods in use.

Change in the amount of an excipient

Goods may be grouped when the formulation of the new goods is to be changed by increasing or decreasing the amount of an excipient (but not adding or deleting an excipient) and when the new goods are to replace the existing goods in use.
Removal or addition of a fragrance, flavour, printing ink or colour

Goods may be grouped when the formulation is changed by the addition or removal of a fragrance, flavour, printing ink or colouring agent and when the new goods are to be registered in place of the existing goods.

Revised indications and/or directions for use

Goods may be grouped when only the indications and/or directions for use are changed and the new goods are to be registered in place of the existing goods.

Changes table codes

The following codes should be read in conjunction with the Changes table (below). Assurances should be made in writing, signed and dated by an authorised person, and should accompany the variation form. Note that the exact wording, as given here, should be used. Failure to make the relevant assurances that are required for notifiable changes may render the change approvable.

Status codes

NEW New application for registration required.
A Prior approval required before proceeding with the change.
N Notification to the Non-Prescription Medicines Branch before proceeding with the change, provided that the required supporting documentation has been supplied.
O No prior approval or notification required. Changes with status 'O' have been included for completeness and do not imply that this information is required for evaluation of an equivalent new product.
ASK Contact OTC Medicines Section

Documentation and assurance codes

E Evidence to support the change where an ARTG entry is to be corrected.
G GMP pre-clearance certificate
L A copy of the current label of the goods plus a draft copy of the new label, with the relevant changes highlighted, have been supplied.
T The submission is accompanied by written requests to effect the change from both the existing and the proposed sponsors.
PI A copy of the current Product Information (PI) of the goods plus a draft copy of the new PI, with the relevant changes highlighted, have been supplied.
P The SUSDP schedule (or 'N' for unscheduled goods) for the new pack size(s) is/are stated in the application form.

1. The ‘new’ goods are intended to replace the existing goods in use.
2. The only difference between the ‘new’ goods and the existing goods is the name.
3. The only differences between the ‘new’ goods and the existing goods are related to the indications for use and/or the directions for use.
4. No additional indications have been introduced or directions for use altered (other than change to wording).
5. No aspects of the labelling, PI, CMI, pharmaceutical data or other product details have been changed or are to be changed, other than changes nominated in this application and those made in conformity with the ‘Changes table’. 
6. The labelling for the new pack size is unchanged, other than to indicate the new pack size number/volume.

7. The only changes made are those which bring the label into compliance with requirements of the Labelling Order\(^5\), or Schedule 2 to the Therapeutic Goods Regulations.

8. The change is in compliance with a requirement introduced in the most recent version or amendment of the Standard for the Uniform Scheduling of Drugs and Poisons.

9. The nominated manufacturer is licensed to manufacture goods of this type.

10. The container type (as defined in TGA Approved Terminology for Drugs) is unchanged and container material is unchanged.

11. A stability testing protocol has been approved for this product and a copy of the approval letter is attached.

12. a) Neither the existing nor the new material is a modified starch; and
   b) The changeover has been validated; and
   c) At least 6 month's stability data have been generated at the maximum recommended storage temperature on product manufactured using the new type of starch, or 3 month's data at a temperature at least 10°C higher than the maximum recommended storage temperature; and
   d) Stability testing will continue for the full term of the product's shelf life and any batches not meeting specifications will be withdrawn from the market immediately and the Non-Prescription Medicines Branch notified immediately.

13. a) The changeover has been validated and the sponsor is satisfied that the change will not adversely affect the stability of the product; and
   b) Stability testing will continue for the full term of the product's shelf life and the TGA advised immediately of any batches not meeting specifications.

14. No new text or graphics have been introduced.

15. The change of material is one of the following:
   a) Polystyrene to PVC, polyethylene, polypropylene or glass;
   b) PVC to polyethylene, polypropylene or glass;
   c) Polyethylene to glass or polypropylene of density 0.89;
   d) From one density of polyethylene to a higher density; or
   e) Any change between glass, polyethylene of density 0.95, and polypropylene of density 0.89.

16. The new container/closure system has demonstrated equal or better moisture protection in the USP test for Containers Permeation (water vapour transmission) to that of the existing container/closure system.

17. The information on the container label is not less than the information on the primary pack.

18. The change to the plastic component is one of the following:
   a) PVC to PVC/PVDC or to PVC/PCTFE;
   b) PVC/PVDC to PVC/PCTFE.

or the change to the plastic component is to a material with demonstrated lower or equivalent water permeability than the existing material (see for example USP monograph '<671> Containers Permeation').

19. Manufacturing method and specifications, other than visual identification, have not been changed.

20. Two production batches have been tested according to the approved stability protocol and all results fall within the acceptance criteria, as specified in the approved stability protocol.

21. The changes are in accordance with s.9D(1) of the Therapeutic Goods Act 1989.
# Changes Table

<table>
<thead>
<tr>
<th>Label changes (including package insert)</th>
<th>Status</th>
<th>A/D*</th>
</tr>
</thead>
<tbody>
<tr>
<td>GPN  Proprietary name (if grouping applies)</td>
<td>A</td>
<td>1, 2, L</td>
</tr>
<tr>
<td>PIN  Proprietary name (if grouping doesn't apply)</td>
<td>NEW</td>
<td>-</td>
</tr>
<tr>
<td>GIN  New therapeutic indications (if grouping applies)</td>
<td>A</td>
<td>1, 3, L</td>
</tr>
<tr>
<td>PTI  New therapeutic indications (if grouping doesn't apply)</td>
<td>NEW</td>
<td>-</td>
</tr>
<tr>
<td>LIW  Therapeutic indications or directions for use – change of wording without altering meaning</td>
<td>A</td>
<td>4, L</td>
</tr>
<tr>
<td>LIS  Therapeutic indications – removal of sub-set of indications from label</td>
<td>N</td>
<td>5, L</td>
</tr>
<tr>
<td>LIR  Therapeutic indications – addition of registered indications to label</td>
<td>A</td>
<td>5, L</td>
</tr>
<tr>
<td>GDU  Directions for use – eg. dosage instructions (if grouping applies) (See also LIW)</td>
<td>A</td>
<td>1, 3, L</td>
</tr>
<tr>
<td>LDU  Directions for use (if grouping doesn't apply)</td>
<td>NEW</td>
<td>-</td>
</tr>
<tr>
<td>PSC  Recommended storage conditions – more restrictive</td>
<td>N</td>
<td>5</td>
</tr>
<tr>
<td>PST  Recommended storage conditions – less restrictive</td>
<td>A</td>
<td>-</td>
</tr>
<tr>
<td>LSR  Addition of more restrictive safety-related statements</td>
<td>N</td>
<td>5, L</td>
</tr>
<tr>
<td>LSF  Changes on label (signal headings, warning statements) in compliance with new SUSDP requirements, where the change in scheduling is from 'Prescription Only Medicine' (Schedule 4) to a lower schedule</td>
<td>A</td>
<td>-</td>
</tr>
<tr>
<td>LSU  Changes on label (signal headings, warning statements) in compliance with new SUSDP requirements, other than LSF</td>
<td>N</td>
<td>5, 8, L</td>
</tr>
<tr>
<td>LLO  Changes to bring a label into compliance with the Labelling Order – other than changes to the proprietary name, indications or directions for use</td>
<td>N</td>
<td>5, 7, L</td>
</tr>
<tr>
<td>LLR  Addition of a required representation to a label (Part 2 of Schedule 2 to the Therapeutic Goods Regulations)</td>
<td>N</td>
<td>5, 7, L</td>
</tr>
<tr>
<td>LCF  Colour, font, type size only (no change in label copy)</td>
<td>N</td>
<td>5, L</td>
</tr>
<tr>
<td>LGR  Introduction of new graphics/icons (other than as specified in change SSP)</td>
<td>A</td>
<td>-</td>
</tr>
<tr>
<td>LFO  Reformatting of pre-existing text (ie. moving of blocks of text and not rewording – see LIW, LRT)</td>
<td>N</td>
<td>5, L</td>
</tr>
</tbody>
</table>

* A/D = assurances to be given and supporting documentation required for the given status to apply. Refer to Changes table codes for an explanation of all codes used.
### Label changes (including package insert)

<table>
<thead>
<tr>
<th>Status</th>
<th>A/D*</th>
</tr>
</thead>
<tbody>
<tr>
<td>LRT</td>
<td>Rewording of pre-existing text without altering meaning (other than indications or directions for use – see LIW)</td>
</tr>
<tr>
<td>LDT</td>
<td>Deletion or addition of text to the label (eg. addition or removal of claims such as <em>clinically proven, fast/rapid action</em>; general claims regarding the product, its nature, mechanism of action, qualifying statements, etc)</td>
</tr>
<tr>
<td>LOC</td>
<td>Other changes</td>
</tr>
</tbody>
</table>

### Sponsor changes

<table>
<thead>
<tr>
<th>Status</th>
<th>A/D*</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSP</td>
<td>Sponsor name/logo(same sponsor of goods) and/or change to manufacturer/supplier details on label</td>
</tr>
<tr>
<td>SAD</td>
<td>Sponsor address</td>
</tr>
<tr>
<td>STR</td>
<td>Transfer goods to another sponsor</td>
</tr>
</tbody>
</table>

### Product detail changes

<table>
<thead>
<tr>
<th>Status</th>
<th>A/D*</th>
</tr>
</thead>
<tbody>
<tr>
<td>GPN</td>
<td>Proprietary name (if grouping applies)</td>
</tr>
<tr>
<td>PIN</td>
<td>Proprietary name (if grouping doesn't apply)</td>
</tr>
<tr>
<td>PSZ</td>
<td>Pack size – other than liquids/semi-solids (see PLS) or metered dose aerosols (see PMZ) (see also KBT, KGL, KBL and KOT)</td>
</tr>
<tr>
<td>PLS</td>
<td>Pack size – liquids/semi-solids</td>
</tr>
<tr>
<td>PMZ</td>
<td>Pack size – metered dose aerosols</td>
</tr>
<tr>
<td>GIN</td>
<td>New therapeutic indications (if grouping applies)</td>
</tr>
<tr>
<td>PTI</td>
<td>New therapeutic indications (if grouping doesn't apply)</td>
</tr>
<tr>
<td>PDF</td>
<td>Dosage form (as defined in TGA Standard Terminology&lt;sup&gt;6&lt;/sup&gt;)</td>
</tr>
<tr>
<td>PVI</td>
<td>Visual identification</td>
</tr>
<tr>
<td>PSL</td>
<td>Shelf life – increase (other than in change PSP)</td>
</tr>
<tr>
<td>PSR</td>
<td>Shelf life – decrease</td>
</tr>
<tr>
<td>PSP</td>
<td>Shelf life – increase (in accordance with an approved stability testing protocol for that product)</td>
</tr>
<tr>
<td>PPR</td>
<td>Approval of a stability testing protocol for a specific product</td>
</tr>
<tr>
<td>PSC</td>
<td>Recommended storage conditions – more restrictive</td>
</tr>
<tr>
<td>PST</td>
<td>Recommended storage conditions – less restrictive</td>
</tr>
<tr>
<td>PMI</td>
<td>Sterility status/technique</td>
</tr>
</tbody>
</table>

---


* A/D = assurances to be given and supporting documentation required for the given status to apply. Refer to [Changes table codes](#) for an explanation of all codes used.
Formulation changes - active ingredients

<table>
<thead>
<tr>
<th>Status</th>
<th>A/D*</th>
</tr>
</thead>
<tbody>
<tr>
<td>AAI</td>
<td>Addition of active ingredient</td>
</tr>
<tr>
<td>AAD</td>
<td>Deletion of active ingredient</td>
</tr>
<tr>
<td>AAA</td>
<td>Amount of an active ingredient (see also Actives/excipients – variations in weight per batch in Chapter 4B, Formulation)</td>
</tr>
<tr>
<td>AOV</td>
<td>Overage – decrease</td>
</tr>
<tr>
<td>AOA</td>
<td>Overage – increase</td>
</tr>
<tr>
<td>GPA</td>
<td>Change to amount of an excipient ingredient within a proprietary ingredient which contains an active substance (e.g. a direct-compression paracetamol mix) (if grouping applies)</td>
</tr>
<tr>
<td>API</td>
<td>Change to a proprietary ingredient which contains an active ingredient, other than as above in change GPA</td>
</tr>
</tbody>
</table>

Formulation changes - excipient ingredients

<table>
<thead>
<tr>
<th>Status</th>
<th>A/D*</th>
</tr>
</thead>
<tbody>
<tr>
<td>GPI</td>
<td>Removal and/or addition of a fragrance, flavour, printing ink or colouring agent (if grouping applies), other than change ERT</td>
</tr>
<tr>
<td>ERE</td>
<td>Removal or addition of a fragrance, flavour, printing ink or colouring agent (if grouping doesn’t apply)</td>
</tr>
<tr>
<td>ERT</td>
<td>Removal of fragrance, flavour, printing ink and/or colouring agent(s) if the total agent(s) are present at not more than 2% w/w or w/v (if grouping applies)</td>
</tr>
<tr>
<td>Note: This change may result in consequential changes (e.g. deletion from the label of declared ingredients that are no longer relevant; change to visual identification and finished product specifications) which should also be addressed in accordance with the ‘Changes Table’.</td>
<td></td>
</tr>
<tr>
<td>EAD</td>
<td>Addition of excipient other than those above in change GPI</td>
</tr>
<tr>
<td>EDE</td>
<td>Deletion of excipient other than those above in change GPI</td>
</tr>
<tr>
<td>GEX</td>
<td>Amount of excipient (if grouping applies)</td>
</tr>
<tr>
<td>EAM</td>
<td>Amount of excipient (if grouping doesn’t apply – see also Actives/excipients – variations in weight per batch in Chapter 4B, Formulation)</td>
</tr>
<tr>
<td>EST</td>
<td>Type of starch</td>
</tr>
<tr>
<td>EWI</td>
<td>Change to ingredients within a proprietary ingredient which is a flavour, fragrance, printing ink or colour (proprietary ingredient has same name)</td>
</tr>
<tr>
<td>EWA</td>
<td>Change to ingredients within a proprietary ingredient which is an excipient (other than above in change EWI)</td>
</tr>
</tbody>
</table>

* A/D = assurances to be given and supporting documentation required for the given status to apply. Refer to Changes table codes for an explanation of all codes used.
<table>
<thead>
<tr>
<th>Quality control changes – finished product specifications</th>
<th>Status</th>
<th>A/D*</th>
</tr>
</thead>
<tbody>
<tr>
<td>QFX Specification ranges – more restrictive</td>
<td>O</td>
<td>-</td>
</tr>
<tr>
<td>QFE Specification ranges – less restrictive</td>
<td>A</td>
<td>-</td>
</tr>
<tr>
<td>QFT Addition of an extra test</td>
<td>O</td>
<td>-</td>
</tr>
<tr>
<td>QFU Deletion of an existing test</td>
<td>A</td>
<td>-</td>
</tr>
<tr>
<td>QFA Analytical method – to comply with amendments to a standard (e.g. the BP or a Therapeutic Goods Order)</td>
<td>O</td>
<td>-</td>
</tr>
<tr>
<td>QFB Analytical method – which has been demonstrated to maintain or improve analytical performance (accuracy, precision and/or specificity)</td>
<td>O</td>
<td>-</td>
</tr>
<tr>
<td>QFC Analytical method – other than as specified above in change QFB</td>
<td>A</td>
<td>-</td>
</tr>
<tr>
<td>QFS Expiry specification ranges following changes to the BP or the General standard for tablets pills and capsules or changes to the USP where a USP monograph has been approved by the TGA in relation to the product</td>
<td>O</td>
<td>-</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Quality control changes - starting material specifications</th>
<th>Status</th>
<th>A/D*</th>
</tr>
</thead>
<tbody>
<tr>
<td>QSX Range – more restrictive</td>
<td>O</td>
<td>-</td>
</tr>
<tr>
<td>QSE Range – less restrictive</td>
<td>A</td>
<td>-</td>
</tr>
<tr>
<td>QST Addition of an extra test</td>
<td>O</td>
<td>-</td>
</tr>
<tr>
<td>QSU Deletion of an existing test</td>
<td>A</td>
<td>-</td>
</tr>
<tr>
<td>QSA Analytical method – to comply with amendments to a standard (i.e. the BP, EP, USP or a Therapeutic Goods Order)</td>
<td>O</td>
<td>-</td>
</tr>
<tr>
<td>QSB Analytical method – which has been demonstrated to maintain or improve analytical performance (accuracy, precision and/or specificity)</td>
<td>O</td>
<td>-</td>
</tr>
<tr>
<td>QSC Analytical method – other than as specified above in change QSB</td>
<td>A</td>
<td>-</td>
</tr>
<tr>
<td>QSM Manufacturer of starting material (specifications unchanged)</td>
<td>O</td>
<td>-</td>
</tr>
<tr>
<td>QSS Supplier of starting material</td>
<td>O</td>
<td>-</td>
</tr>
</tbody>
</table>

* A/D = assurances to be given and supporting documentation required for the given status to apply. Refer to Changes table codes for an explanation of all codes used.
### Packaging Changes

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
<th>Status</th>
<th>A/D*</th>
</tr>
</thead>
<tbody>
<tr>
<td>KCT</td>
<td>Container type (as defined in TGA Standard Terminology)</td>
<td>NEW</td>
<td>-</td>
</tr>
<tr>
<td>KBT</td>
<td>Container material – if the container is a bottle, the goods are a solid dosage form (eg. tablet) and the change is of a type listed in assurance 15</td>
<td>N</td>
<td>5, 10, 13, 15 &amp; 16</td>
</tr>
<tr>
<td>KGL</td>
<td>Container material – clear to coloured glass</td>
<td>O</td>
<td>-</td>
</tr>
<tr>
<td>KBL</td>
<td>Container material – if the container is a blister pack, the goods are a solid dosage form (eg. tablet) and the change is of a type listed in assurance 18</td>
<td>N</td>
<td>5, 10, 13 &amp; 18</td>
</tr>
<tr>
<td>KOT</td>
<td>Container material – other than in changes KBT, KGL or KBL</td>
<td>A</td>
<td>-</td>
</tr>
<tr>
<td>KCL</td>
<td>Closure</td>
<td>N</td>
<td>5, 13</td>
</tr>
<tr>
<td>KSL</td>
<td>Tamper evident seal – addition (including label notice to alert consumers to presence of seal)</td>
<td>O</td>
<td>-</td>
</tr>
<tr>
<td>KSX</td>
<td>Tamper evident seal – removal (including removal of label notice re seal)</td>
<td>O</td>
<td>-</td>
</tr>
<tr>
<td>KWA</td>
<td>Inert wadding material – addition, substitution or removal where stability is not affected by the action</td>
<td>O</td>
<td>-</td>
</tr>
<tr>
<td>KDA</td>
<td>Desiccant – inclusion in container</td>
<td>A</td>
<td>-</td>
</tr>
<tr>
<td>KDX</td>
<td>Desiccant – removal from container</td>
<td>A</td>
<td>-</td>
</tr>
<tr>
<td>KPP</td>
<td>Specifications of primary pack (other than labelling)</td>
<td>O</td>
<td>-</td>
</tr>
<tr>
<td>KSP</td>
<td>Introduction of a measuring device (eg. spoon, cylinder) or applicator (eg. finger cot)</td>
<td>N</td>
<td>5</td>
</tr>
<tr>
<td>KMD</td>
<td>Changes to existing measuring device (eg. spoon, cylinder) or applicator supplied with the goods or removal of a measuring device or applicator, where other means of accurately measuring or applying the dose are readily available</td>
<td>N</td>
<td>5</td>
</tr>
<tr>
<td>KPA</td>
<td>Introduction of a primary pack (no new text or graphics)</td>
<td>N</td>
<td>5, 14</td>
</tr>
<tr>
<td>KPI</td>
<td>Introduction of a package insert</td>
<td>A</td>
<td>-</td>
</tr>
<tr>
<td>KRI</td>
<td>Removal of a package insert</td>
<td>A</td>
<td>-</td>
</tr>
<tr>
<td>KPX</td>
<td>Removal of a primary pack</td>
<td>N</td>
<td>5, 17</td>
</tr>
<tr>
<td>KRP</td>
<td>Introduction of a refill pack</td>
<td>A</td>
<td>-</td>
</tr>
<tr>
<td>KRR</td>
<td>Removal of refill pack</td>
<td>N</td>
<td>-</td>
</tr>
</tbody>
</table>

*A/D = assurances to be given and supporting documentation required for the given status to apply. Refer to Changes table codes for an explanation of all codes used.*
<table>
<thead>
<tr>
<th>Manufacturing changes – finished product</th>
<th>Status</th>
<th>A/D*</th>
</tr>
</thead>
<tbody>
<tr>
<td>TGA licensed Australian manufacturer (includes site of manufacture)</td>
<td>N</td>
<td>5, 9</td>
</tr>
<tr>
<td>Overseas manufacturer (includes site of manufacture), if GMP pre-clearance certificate provided</td>
<td>N</td>
<td>5, G</td>
</tr>
<tr>
<td>Overseas manufacturer (includes site of manufacture), if GMP pre-clearance not provided</td>
<td>A</td>
<td>-</td>
</tr>
<tr>
<td>Manufacturing process (other than MBS)</td>
<td>N</td>
<td>13</td>
</tr>
<tr>
<td>Batch size for pressurised inhalation (nasal and oral respiratory) products</td>
<td>A</td>
<td>-</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Consumer Medicine Information CMI</th>
<th>Status</th>
<th>A/D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Introduction of a CMI for a ‘Pharmacist Only Medicine’ (Schedule 3) product registered after 4 July 1995 where the CMI complies with Schedule 13 to the <em>Therapeutic Goods Regulations</em> and is not to be included as a package insert. Note: Change KPI applies where the CMI is to be included as a package insert.</td>
<td>O</td>
<td>-</td>
</tr>
<tr>
<td>Changes to an existing CMI, where the changes are consistent with all previously approved product details and the CMI is not to be included as a package insert. Note: Refer to the ‘Label changes’ section for guidance on changes to a CMI where the CMI is to be included as a package insert (package inserts are treated as part of the label).</td>
<td>O</td>
<td>-</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Product Information (PI)</th>
<th>Status</th>
<th>A/D*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Introduction of a PI for an existing product</td>
<td>A</td>
<td>-</td>
</tr>
<tr>
<td>Addition of more restrictive safety-related statements</td>
<td>N</td>
<td>5, PI</td>
</tr>
<tr>
<td>Changes other than the addition of more restrictive safety-related statements</td>
<td>A</td>
<td>-</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other</th>
<th>Status</th>
<th>A/D*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Correction of ARTG record in accordance with section 9D(1) of the <em>Therapeutic Goods Act 1989</em></td>
<td>N</td>
<td>E, 5, 21</td>
</tr>
</tbody>
</table>

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