Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian regulatory guideline for over-the-counter medicines

Appendix 4: Guidelines on OTC application for new substances

Version 1.0, October 2012

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The TGA is part 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 <www.tga.gov.au>.

Version history

Version	Description of change	Author	Effective date
V1.0	Update of ARGOM Chapter 6B New substances. Re-formatting of Chapter 6B as Appendix 4 – Guideline on OTC applications for new substances.	MAG – OTCME	October 2012

Contents

Introduction

This part of the guidance document describes applications and safety data requirements for a new substance intended for use in an over-the-counter (OTC) medicine. It does not describe efficacy requirements, which are described in *Appendix 1 Guidelines on the efficacy and safety aspects of OTC application*[1]. The *Australian Regulatory Guidelines for Over-the-counter Medicines* (ARGOM)[2], Chapter 10 Sunscreens contains specific information on the requirements for new active ingredients intended for use in sunscreens.

The Appendix is divided into four (4) sections as follows:

1. Substances for use in listed OTC medicines
2. Substances for use in registered OTC medicines
3. Submission and approval of substance applications
4. Data requirements

A 'new' substance is one that is not in any product currently on the ARTG for supply in Australia. An excipient which is not included in such products, but had a previous long history of safe use in medicines supplied in Australia, may not be considered as a new excipient provided such use is demonstrated.

A new substance can be included as either a new active or new excipient as part of an application to register a new OTC medicine. Sponsors can also apply to the TGA to determine the suitability of a new substance for use in either Registered OTC medicines or Listed OTC medicines (as specified in Schedule 4 of the Therapeutic Goods Regulations[3]), by submitting a stand-alone 'Substance' application (see 'Section 3 Submission and approval of substance applications').

It is strongly recommended that sponsors consult Schedule 10 of the Therapeutic Goods Regulations 1990 (the 'Regulations') to determine the appropriate route of evaluation for any new substances before applying to the TGA. Information regarding the process for scheduling of new substances in the *Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP)[4] is available on the TGA website[5].

[1] http://www.tga.gov.au/industry/otc-argom-app1.htm
[2] http://www.tga.gov.au/industry/otc-argom.htm
[3] http://www.tga.gov.au/industry/legislation.htm
[4] http://www.tga.gov.au/industry/scheduling-poisons-standard.htm
[5] http://www.tga.gov.au/industry/scheduling-pathway.htm

1. Substances for use in listed OTC medicines

Most common OTC medicines are registrable, but some low-risk OTC medicines, in particular sunscreens, are listable. Where a new substance is proposed for use in a Listed OTC (non-complementary[6]) medicine, the required safety and chemistry data will need to be submitted as part of a "Substance" application (see 'Section 3 Submission and approval of substance applications'). A "Substance" application is also required where a new route of administration for a Listed OTC medicine is proposed for an existing ingredient, or where an existing excipient ingredient is proposed for use in a Listed OTC medicine as an active ingredient for the first time. If approved, the substance may then be used in Listed medicines without the need for submission of further safety data, provided any conditions or limitations on the use of the substance are met (refer to 'Section 3 Submission and approval of substance applications').

> **Note:** While the efficacy of a new active substance is not assessed in a "Substance" application, when listing a new OTC medicine the sponsor must certify that evidence is held in support of any efficacy claims [see the *Australian Regulatory Guidelines for Complementary Medicines* (ARGCM) – Part II[7]]. For further information specifically in relation to ingredients for use in sunscreen, refer to the *Australian Regulatory Guidelines for Over-the-counter Medicines* (ARGOM), Chapter 10 Sunscreens[8].

2. Substances for use in registered OTC medicines

Where a new substance is proposed for use in a Registered medicine, data relating to the new substance are usually provided and assessed as part of the product application, which includes provision and assessment of quality, safety and efficacy data. However, the TGA is also willing to accept an application for 'approval' of a substance in isolation from a product without clinical efficacy data. In these circumstances, the safety of the substance per se will be assessed and the sponsor will be advised of its acceptability or otherwise for use in Registered medicines and of any conditions or limitations that might apply. Future applications to register non-prescription medicines containing the substance will not usually need to include non-clinical data to establish the safety of the approved substance (provided any conditions or limitations on the use of the substance are met – see 'Section 3 Submission and approval of substance applications').

[6] For information regarding requirements for *complementary* medicine substances, refer to the *Australian Regulatory Guidelines for Complementary Medicines* (ARGCM) http://www.tga.gov.au/industry/cm-argcm.htm

[7] http://www.tga.gov.au/industry/cm-argcm.htm

[8] http://www.tga.gov.au/industry/otc-argom.htm

3. Submission and approval of substance applications

Sponsors can apply to have a new substance evaluated by the TGA by completing the "Substance" form in the OTC medicines portal in electronic Business Services (eBS). The TGA requires that sponsors establish the correct regulatory route of evaluation (under Schedule 10 of the Regulations[9]) prior to submitting an application.

Sponsors should use Australian Approved Name (AAN) terminology[10]. For those ingredients without an AAN, an *Application form for proposing a chemical name*, available from the TGA website[11], should be completed and either included with the application or submitted separately to the TGA (to the attention of the 'The Secretariat, Australian Approved Names Committee').

> **Note:** Where the form has been submitted separately, it is recommended that the application letter include a statement alerting the evaluator to this fact or a copy of the AAN application form also be included in the substance application.

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 the substance is proposed for use by a different route of administration or at higher concentrations than have been previously approved.

4. Data requirements

Safety and chemistry data should be provided in a new substance application (see 'Section 4.1 Safety Data' and 'Section 4.2 Chemistry data'). The data requirements to support a new substance for use in a medicine will be dependent on the function of the substance (i.e. active or non-active substance) and route of administration. For new active substances and novel excipients, comprehensive safety data are required (see 'Section 4.1.1 Active substance and novel excipients'). Where an excipient has a well documented safety profile and extensive experience of use in humans, a literature-based submission and scientific justifications may be appropriate (see 'Section 4.1.2 Well documented excipients'). In the case of topical excipients, an abbreviated data package is acceptable (see 'Section 4.1.3 Topical excipients').

For new alternative pharmaceutical forms (e.g. salts, esters) of existing approved ingredients, data requirements for new substances may apply if safety or efficacy properties are likely to be different. In some cases, where justified, bioequivalence data, or a justification for not providing such data, may be sufficient.

In some circumstances, data requirements applying to new substances may also apply where a new route of administration is proposed for an existing substance (e.g. when an excipient that is only included in topical products is proposed for use in an oral product) or, for Listed medicines, where an excipient ingredient is proposed for use as an active ingredient (see 'Section 1 Substances for use in listed OTC medicines').

[9] http://www.tga.gov.au/industry/legislation.htm
[10] http://www.tga.gov.au/industry/medicines-approved-terminology.htm
[11] http://www.tga.gov.au/industry/medicines-approved-terminology.htm#forms

In addition to the safety and chemistry data, details should be provided of the types of products the substance is intended to be included in. The intended dosage form and amount (maximum and minimum), route of administration, frequency and basis of calculation of these should also be given. For substances intended as active ingredients, the therapeutic claims intended for products containing the substance and pharmacological activities of the substance should be included, as the safety evaluation may need to be considered in the context of the intended use of the substance. However, clinical efficacy will not be evaluated as part of a "Substance" application. For substances with potential effects on the bioavailability of other ingredients, particularly active ingredients, data on the effects on model ingredients or specific active ingredients may be included.

Information on the regulatory status of the new substance in other countries should be provided. If an application for approval has been rejected or withdrawn prior to approval, or withdrawn (e.g. due to adverse effects) following marketing approval, this should be noted in the application. Details of the approved use of the substance (e.g. in therapeutic goods, food, cosmetics) and any restrictions on its use should be provided where appropriate. It should be noted that a substance's use as a food may assist in the safety assessment but not in establishing validity of the therapeutic claims. Precise nomenclature for the substance registered, used or approved overseas should be provided.

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 exposures.

A number of countries (USA, Canada, Sweden, The Netherlands and the UK) have similar regulatory systems to Australia for the evaluation of therapeutic goods. 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 may be provided to expedite the evaluation by the TGA.

For active substances, unless there is evidence of safety in pregnant or lactating women, products containing the substance may be required to carry an appropriate warning (e.g. "Do not use if you are pregnant or may become pregnant or are breastfeeding"). Any additional risks to consumers who abuse the substance, such as taking doses many times greater than recommended, or by consuming them in association with antagonistic products, should be noted and addressed, as relevant.

The data requirements described in this appendix are flexible and not prescriptive. Approval may be based on the evaluation of a data package containing published and/or sponsor generated studies provided omissions/variations are appropriately and scientifically justified.

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

4.1 Safety data

The safety of a new substance should be adequately assessed by non-clinical and/or clinical studies. Toxicological studies in support of an application for a new substance should be carried out using the substance in the chemical form (e.g. a salt or an ester) intended for use in the marketed product. Variations in chemical form should be justified and their use in any studies should be clearly indicated.

4.1.1 Active substances and novel excipients

For new active substances and novel excipients, safety data requirements are the same as for new active substances in prescription medicines [see *Australian Regulatory Guidelines for Prescription Medicines* (ARGPM)[12]]. Data consistent with the requirements of the European Union (EU) guidelines relevant to the assessment of a 'new chemical entity (NCE)' in prescription medicines should be provided. The EU guidelines adopted by the TGA are detailed on the TGA website[13]. For non-clinical studies, the most relevant guideline is the *Guidance on non-clinical safety studies for the conduct of human clinical trials and marketing authorisation for pharmaceuticals*[14]. This guideline and other relevant guidelines can be found under Non-clinical Guidelines[15] in the sections covering pharmacology, pharmacokinetics and toxicology. Non-clinical data requirements include:

- pharmacodynamic/pharmacokinetic and toxicokinetic studies addressing the pharmacological activity and pharmacokinetic behaviour and systemic exposure of the substance; AND
- safety studies addressing acute toxicity, repeat-dose toxicity, carcinogenicity, genotoxicity reproductive toxicity, local tolerance, and, where appropriate, other studies (e.g. immunotoxicity, photosafety).

Non-clinical safety studies (toxicity and toxicokinetic studies) should be carried out in accordance with Organisation for Economic Co-operation and Development (OECD) or FDA guidelines of good laboratory practice [*OECD Principles on good laboratory practice (GLP) and Compliance Monitoring*[16]*; Good Laboratory Practice for Nonclinical Laboratory Studies 21CFR58*[17]]. Studies should be identified as having quality assurance from the laboratory where the study was carried out and be signed by the study director.

Studies need to include clear, legible tabulation and a descriptive presentation of the methodologies and findings as well as individual animal data for validation of the results. Each of the study types should be supported by appropriate data or scientifically validated justification.

Pharmacokinetic 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. Toxicokinetic data supporting the route of administration used in key toxicity studies (e.g. intended usage route) should be provided.

The sponsor should submit all relevant and appropriate data (company and contract laboratory studies, etc) on the substance. Studies which were carried out pre-GLP may not be suitable for evaluation but may be provided as supporting data. Information from Periodic Safety Update Reports (PSURs) may be included.

[12] http://www.tga.gov.au/industry/pm-argpm.htm
[13] http://www.tga.gov.au/industry/pm-euguidelines-adopted.htm
[14] http://www.tga.gov.au/industry/pm-euguidelines-adopted-nonclinical.htm#nonclinicaltoxicology
[15] http://www.tga.gov.au/industry/pm-euguidelines-adopted-nonclinical.htm
[16] http://www.oecd.org/document/63/0,2340,en_2649_34381_2346175_1_1_1_1,00.html
[17] http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=58&showFR=1

4.1.2 Well documented excipients

For substance with a well documented safety profile and extensive experience of use in humans in other countries, a literature-based submission (LBS) may be appropriate (see *ARGOM Appendix 1 Guidelines on efficacy and safety aspects of OTC application: Section 2 Literature-based submissions*)[18]. In this instance, the *Register of Toxic Effects of Chemical Substances* (RTECS)[19], Toxnet (Toxline)[20], *Medline*[21] or *Embase*[22] (Excerpta Medica) would be acceptable databases on which to base a literature search. Full copies of all cited references, databases searched and search strategies should be submitted to enable validation of the literature search methodology and results.

The literature may include chapters from reference and text books in addition to peer-reviewed journal articles and should address the pharmacodynamic and pharmacokinetic behaviour and toxicity as required for active substances and novel excipients (see 'Section 4.1.1 Active substances and novel excipients').

In circumstances where a literature-based submission is not appropriate it will be necessary to provide reports of sponsor-generated non-clinical studies and, if available clinical data or scientific justifications.

Any known, potential or suspected adverse effects should be noted.

4.1.3 Topical excipients

For topical excipients with established clinical use history, an abbreviated data package is acceptable (see the *Australian Regulatory Guidelines for OTC Medicines* (ARGOM 2003), Chapter 10 Sunscreens[23]). It should be noted that additional studies may be requested in individual cases where safety concerns become evident at the time of evaluation.

4.2 Chemistry data

Chemistry data requirements for new substances are generally the same as those for prescription medicines and reference should be made to the *Australian Regulatory Guidelines for Prescription Medicines* (ARGPM)[24]. However, for complex substances (e.g. complex herbal extracts), the *Australian Regulatory Guidelines for Complementary Medicines* (ARGCM)[25] may also be relevant. For new topical excipient ingredients, sponsors generally need only provide a full description of the substance (including chemical structure, physical properties, CAS number, molecular weight, molecular formula and nomenclature, where appropriate).

[18] http://www.tga.gov.au/industry/otc-argom-app1.htm
[19] http://ccinfoweb.ccohs.ca/rtecs/search.html
[20] http://toxnet.nlm.nih.gov
[21] http://www.nlm.nih.gov/databases/databases_medline.html
[22] http://www.embase.com/info/what-is-embase
[23] http://www.tga.gov.au/industry/otc-argom.htm
[24] http://www.tga.gov.au/industry/pm-argpm.htm
[25] http://www.tga.gov.au/industry/cm-argcm.htm

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