Australian Government
Department of Health
Therapeutic Goods Administration

OTC medicines – Safety and efficacy data

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TGA Health Safety Regulation

Contents

Introduction ____ 4

1 - Specific OTC medicines ____ 4

1.1 Higher risk medicines ____ 4

1.2 Nicotine replacement therapy ____ 4

1.3 Other specific medicines ____ 4

2 - OTC generic medicines ____ 5

2.1 Generic oral medicines ____ 5

2.2 Generic topical (locally acting, locally applied) medicines ____ 8

2.3 Generic modified release dosage forms ____ 10

3 - OTC non-generic medicines ____ 11

3.1 Non-generic topical (locally acting, locally applied) medicines ____ 12

3.2 Active ingredients in a new dosage form ____ 12

3.3 New fixed combination medicines ____ 12

3.4 New modified release dosage forms ____ 13

4 - Types of data to support OTC medicine applications 14

4.1 Literature-based submissions ____ 14

4.2 Clinical trial reports ____ 15

4.3 Non-clinical studies ____ 15

4.4 Post-market information ____ 16

5 - Legislative basis for safety and efficacy data ____ 17

5.1 Registering a new medicine in the ARTG ____ 17

5.2 Varying a medicine included in the ARTG ____ 17

Introduction

This guidance describes the safety and efficacy data you will need for CTD Module 4 and Module 5 to support applications to either:

- register an OTC medicine in the ARTG
- vary the safety and/or efficacy aspects of a registered OTC medicine.

For guidance on how to present clinical efficacy and safety data in the CTD format, see:

- *CTD for the registration of pharmaceuticals for human use - clinical overview* and clinical summary of Module 2 and Module 5: EU Module 5 - Clinical Studies (CPMP/ICH/2887/99 Rev 1 Efficacy)
- *CTD for the registration of pharmaceuticals for human use - Nonclinical overview* and nonclinical summaries of Module 2 and organisation of Module 4: EU Module 4 - Nonclinical studies (CPMP/ICH/2887/99 Rev 1 Safety)

1 - Specific OTC medicines

1.1 Higher risk medicines

The following higher risk OTC medicines are evaluated via the Prescription medicine pathway:

- medicines containing oral nitrates for the treatment of heart disease
- nasal corticosteroids and metered dose asthma inhalers
- new transdermal patches (e.g. nicotine patches)

Refer to Guidance 19: Inhalation and nasal medicines for guidance on nasal corticosteroids and metered dose asthma inhalers.

Follow the prescription medicine registration process and submit data in accordance with the Australian Regulatory Guidelines for Prescription Medicines (ARGPM).

1.2 Nicotine replacement therapy

Refer to Nicotine replacement therapy (NRT) for specific guidance on safety and efficacy data for NRT medicines.

1.3 Other specific medicines

Refer to ARGOM Appendix 5: Guidelines on OTC applications for specific substances for guidance on safety and efficacy data requirements for various specific OTC medicines.

2 - OTC generic medicines

In most cases you do not need to provide safety or efficacy data in support of OTC generic medicines. However, in some cases you may need to provide bioequivalence data or therapeutic equivalence data to demonstrate bioequivalence or therapeutic equivalence with the originator medicine.

To determine if you need to provide bioequivalence or therapeutic equivalence data:

- for **oral medicines** go to Generic oral medicines
- for **topical medicines** go to Generic topical (locally acting, locally applied) medicines

In rare cases where supporting data for the originator medicine are 'protected', we require full efficacy and safety data. This applies where the active ingredient was first included in an Australian medicine within the last five years (Section 25A of the *Therapeutic Goods Act 1989* refers).

2.1 Generic oral medicines

When bioequivalence data (or justification) are not required

You do not need to provide bioequivalence data, or a justification for not providing this data, if any of the following apply:

- The medicine is an oral medicine and there are other corresponding OTC generic medicines registered on the ARTG that have been approved without either:
  - bioequivalence data (not including N1 application approvals)
  - a justification for not providing bioequivalence data.

  The large number of OTC medicines that fall into this category are detailed under Generic oral medicines that do not require bioequivalence data.
- The medicine is an aqueous oral solution at the time of administration and both:
  - the active substance is in the same concentration as a currently registered oral solution
  - the excipients do not significantly affect: gastric passage or absorption of the active substance or *in vivo* solubility or *in vivo* stability of the active substance (provide justification or evidence to support this).
- The medicine is an oral medicine containing active ingredients that are not absorbed (e.g. barium sulphate, simethicone and alginic acid).
- The medicine is for oral topical use and is intended to act without systemic absorption. However, you may need to provide therapeutic equivalence data - see Generic topical (locally acting, locally applied) medicines.
- The medicine differs from a fully evaluated and registered medicine only by way of a minor difference in formulation of the colouring agents, printing inks, flavours or fragrances, that are present at not more than 2% w/w/ or w/v (e.g. a new flavour being added to an existing range).
- The medicine has an acceptable correlation between the rate and extent of *in vivo* absorption and the *in vitro* dissolution rate, and the *in vitro* dissolution rate of the new medicine is equivalent (under the same test conditions used to establish the correlation) to a registered medicine.

Generic oral medicines that do not require bioequivalence data

Unless the exceptions below apply, you do not need to provide bioequivalence data (or a justification for not providing this data) for generic immediate release or enteric coated oral dose form medicines (e.g. tablet, capsule, oral liquid or suspension) that only contain one or more of the following active ingredients:

- Aspirin
- Bisacodyl
- Bromhexine hydrochloride
- Brompheniramine maleate
- Caffeine
- Chlorpheniramine maleate
- Codeine phosphate
- Dexchlorpheniramine maleate
- Dextromethorphan hydrobromide
- Dimenhydrinate
- Diphenhydramine hydrochloride
- Docusate sodium
- Doxylamine succinate
- Guaiphenesin
- Hyoscine butylbromide
- Hyoscine hydrobromide
- Ibuprofen
- Ibuprofen lysine
- Ibuprofen sodium
- Loperamide hydrochloride
- Mebendazole
- Naproxen
- Naproxen sodium
- Paracetamol
- Phenylephrine hydrochloride
- Promethazine hydrochloride
- Pseudoephedrine hydrochloride
- Ranitidine hydrochloride

- Sennosides
- Triprolidine hydrochloride

Exceptions

Even if the ingredient is listed above, you will still need to provide bioequivalence or other clinical data (or a justification for not providing such data) when:

- your application includes a request for a brand equivalence statement for the purposes of Pharmaceutical Benefits Scheme (PBS) listing.
- there is reason to consider that bioavailability of the medicine differs from existing medicines so as to adversely impact on efficacy and/or safety (e.g. it contains excipient(s) or has novel properties that could significantly affect gastric passage, absorption, in vivo solubility or in vivo stability of the active substance). Contact OTC Medicines if you are unsure.

Note: If a new originator combination medicine containing active ingredients from the above list was approved, bioequivalence data (or justification for not providing) would be necessary in support of subsequent generic applications.

When bioequivalence data (or justification) are required

Provide bioequivalence data (or a justification for not providing) if your medicine does not meet the criteria described in When bioequivalence data (or justification) are not required. Contact OTC Medicines if you are unsure.

Requirements for bioequivalence studies

Study requirements are described in:

- Biopharmaceutic studies
- *Guideline on the investigation of bioequivalence* (CPMP/EWP/QWP/1401/98 Rev 1); adopted by the TGA with annotations

Include biopharmaceutic study reports in CTD Module 5.3.1.

Complete the *Summary of a Bioavailability or Bioequivalence Study* form for each study and include in CTD Module 1.11.1.

Choice of reference medicine

You will need to demonstrate bioequivalence against the corresponding strength of the originator medicine as marketed in Australia. If you are unsure of the identity of the originator medicine, contact OTC Medicines.

We will accept bioequivalence studies carried out using samples of the originator medicine obtained from outside Australia if you, as the applicant, can provide robust scientific evidence that the overseas and Australian reference products are identical. See Biopharmaceutic studies for details of the evidence required.

Justifications for not providing bioequivalence data

Include a justification if you are not providing bioequivalence data when it would normally be required.

Ensure your justification addresses all issues as outlined in both:

- Biopharmaceutic studies, Section 15.9
- Appendix III of the European Union (EU) *Guideline on the investigation of bioequivalence* (CPMP/EWP/QWP/1401/98 Rev 1).

Include the justification and copies of any cited literature in CTD Module 1.9.2.

If we do not accept your justification and you subsequently wish to provide bioequivalence or other clinical data, this will need to be provided as part of a new application.

Related information and guidance

For generic OTC medicines that require bioequivalence data:

- ARGPM Guidance 15: Biopharmaceutic studies
- *Guideline on the investigation of bioequivalence* (CPMP/EWP/QWP/1401/98 Rev 1); adopted by the TGA with annotations

2.2 Generic topical (locally acting, locally applied) medicines

The safety and efficacy of topical medicines may be influenced by the excipient formulation. For example, different excipients may significantly affect the release of active substances from the formulation or the penetration of active substances into the skin.

For many OTC topical medicines that have a long history of use, often in a range of different formulations, safety and efficacy can be sufficiently assured and provision of supporting data are not required.

For some generic topical medicines, you will need to demonstrate therapeutic equivalence of the proposed medicine to the originator medicine.

When therapeutic equivalence data are not required

You do not need to provide safety or efficacy (therapeutic equivalence) data for the following topically-applied ingredients or medicine categories, provided the medicine is a true generic (i.e. same strength, pharmaceutical form, directions, indications) and it is conventionally formulated:

- Antibacterial and/or anaesthetic and/or anti-inflammatory throat lozenges (containing amylmetacresol, dichlorobenzyl alcohol, cetylpyridinium chloride, benzydamine hydrochloride, benzocaine, hexylresorcinol, benzyl alcohol, lignocaine hydrochloride)
- Antifungal treatments containing clotrimazole, bifonazole, miconazole, miconazole nitrate, ketoconazole or terbinafine (excluding shampoos and nail treatments)
- Benzoyl peroxide for acne treatment

- Chloramphenicol eye drops
- Decongestant nasal preparations containing oxymetazoline hydrochloride or xylometazoline hydrochloride
- Hydrocortisone or hydrocortisone acetate
- Hydrocortisone-antifungal combinations
- Lignocaine (for superficial pain only, e.g. not for pain of injections)
- Naphazoline eye drops
- Nystatin oral drops
- Potassium nitrate/fluoride desensitising toothpastes/gels
- Povidone-iodine sore throat gargles
- Sodium cromoglycate eye drops

When therapeutic equivalence data are required

For the following topically-applied ingredients or medicine categories, provide data to demonstrate therapeutic equivalence of the medicine to the Australian originator medicine:

- Aciclovir
- Anti-inflammatory sore throat preparations (excluding benzydamine hydrochloride lozenges)
- Antidandruff shampoos containing imidazole antifungals or ciclopirox olamine as active ingredients
- Antifungal nail treatments
- Antiseptics/skin disinfectants
- Corticosteroids (except hydrocortisone and hydrocortisone acetate; see also Specific OTC medicines)
- Dithranol
- Head lice preparations
- Minoxidil
- Non-steroidal anti-inflammatory medicines (NSAIDs)
- Products containing glyceryl trinitrate (see also Specific OTC medicines)

If you are unsure about data requirements

The above lists are not exhaustive and the absence of any ingredient or medicine does not necessarily indicate that safety and efficacy data are, or are not, required - we may simply not have considered the ingredient or medicine in this regard (e.g. for recently down-scheduled ingredients). We will update these lists as further medicines are considered.

Contact OTC Medicines if you are unsure of data requirements.

Therapeutic equivalence data requirements

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

For topical solutions, refer also to Appendix II of *Guideline on the investigation of bioequivalence* (CPMP/EWP/QWP/1401/98 Rev 1).

You will need to demonstrate therapeutic equivalence against the corresponding strength of the originator medicine as marketed in Australia. Refer to Choice of reference medicine.

2.3 Generic modified release dosage forms

Provide supporting data as described in the *Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms* (EMA/CPMP/EWP/280/96 Corr1), Section 6, Abridged application for modified release forms referring to a marketed modified release form.

3 - OTC non-generic medicines

Your medicine is a non-generic if it includes new:

- active ingredients (new chemical entity or NCE)
- active ingredient strengths
- active ingredient combinations
- dosage forms
- indications
- directions

If your medicine is based on an existing medicine that has not been fully evaluated by the TGA (i.e. 'grandfathered'), it is likely to require data as for non-generic medicines. Contact OTC Medicines if you are unsure.

For non-generic medicines you will need to provide data to support efficacy and safety. Data requirements will vary depending on the nature of your proposed medicine. Refer to the following guidance, as relevant:

- TGA medicines guidance
- TGA adopted EU clinical and nonclinical guidelines
- Non-generic topical (locally acting, locally applied) medicines
- Active ingredients in a new dosage form
- New fixed combination medicines
- New modified release dosage forms

Refer also to Types of data to support OTC medicine applications for guidance on the specific types of data that may be required.

If you are unsure as to the data required to support your proposed medicine, contact OTC Medicines.

3.1 Non-generic topical (locally acting, locally applied) medicines

For safety and efficacy data requirements refer to *Note for guidance on clinical requirements for locally applied, locally acting products containing known constituents* (CPMP/EWP/239/95 final).

3.2 Active ingredients in a new dosage form

- If your medicine contains an active ingredient that is new for the proposed dosage form, data requirements will vary depending on the nature of the application, as follows:
- If your medicine involves a **new route of administration** for the active ingredient, provide full clinical and non-clinical studies.
- If your medicine is a **new locally-acting topical dose form** for the active ingredient where others already exist (e.g. a proposed gel form of a currently registered cream), provide full clinical data and local tolerance data unless otherwise justified. Refer to *Note for guidance on clinical requirements for locally applied, locally acting products containing known constituents* (CPMP/EWP/239/95 final).
- If your medicine is a **modified release medicine**, follow the guideline for new modified release dosage forms.
- If your medicine is a **new immediate release oral dose form** for the active ingredient where others already exist (e.g. a proposed tablet form of a registered oral suspension) and qualifies as a generic medicine, follow the guideline for OTC generic medicines. If it is not a generic medicine (e.g. different dosage or indications), provide necessary clinical and/or non-clinical data to support the safety and efficacy of the medicine.

3.3 New fixed combination medicines

Provide supporting data as described in the *Guideline on Clinical Development of Fixed Combination Medicinal Products* (CPMP/EWP/240/95 Rev1).

Refer to the guideline for full requirements. To assist you, we have provided the following points from the guideline:

- The combination should be based on valid therapeutic principles.
- The duration of action of the active ingredients should not differ significantly, unless the combination is clinically valid despite differences in this respect.
- Where the individual active ingredients are intended simultaneously to relieve different symptoms of a particular disease state, these symptoms should regularly occur simultaneously:
  - in a clinically relevant intensity
  - for a relevant period of time.
- The advantages and disadvantages of the combination and each dose of the combination need to be assessed in the justification provided.
- Each dose combination should be carefully justified and clinically relevant.

- The dosage of each active ingredient should be such that:
  - the combination is safe and effective for a significant target population
  - the benefit/risk assessment of the combination is equal to (or exceeds) that of each active ingredient alone.
- Each active ingredient should make a therapeutic contribution to the claimed indications. This should be demonstrated by clinical studies, unless otherwise justified.
- Data should be submitted to establish that pharmacokinetic and pharmacodynamic interactions between the active ingredients either:
  - do not occur
  - are clearly recognised and defined

Composite packs

The requirements for new fixed combination medicines also apply to new composite packs.

3.4 New modified release dosage forms

Provide supporting data as described in the *Guidance on the pharmacokinetic and clinical evaluation of modified release dosage forms* (EMA/CPMP/EWP/280/96 Corr1).

4 - Types of data to support OTC medicine applications

4.1 Literature-based submissions

If you do not have your own supportive data, but have published scientific literature you consider to be supportive of an application, you may opt for a literature based submission (LBS). Examples where this may be appropriate include the following types of applications:

- changes to indications or label claims
- changes to directions for use
- changes to clinical or non-clinical aspects of the Product Information
- new medicine applications (less common).

Mixed applications (part LBS, part complete study reports) may also be appropriate.

Requirements for literature-based OTC medicine submissions

Our OTC requirements for literature based submissions are essentially the same as for prescription medicines except that:

- You do not need to consult or gain approval of LBS search strategies prior to submitting your application.
- We do not have a formal pre-submission phase for OTC medicine applications.

You will need to conduct a systematic literature search for most literature based submissions, including those in support of new indications or label claims.

For further guidance on when an LBS may be suitable and what type of LBS to prepare, refer to the Pre-submission guidance for literature based submissions.

Standard reference texts

For some very old medicines where evidence from published studies is not available to be submitted, the use of standard reference texts such as the Handbook of Non-prescription Drugs (American Pharmacists Association, USA) may be acceptable as part of a LBS not based on a systematic search of the literature.

However, limited clinical reports of efficacy alone or anecdotal reports (e.g. in Martindale "xxx has also been used in …") are not regarded as evidence of safety and efficacy.

If you are unsure of requirements, contact OTC Medicines.

Dossier requirements

Follow the guidance on dossier requirements for literature searches to compile your submission dossier.

Include any advice we give you about your literature search in Module 1.5.1 of the dossier.

4.2 Clinical trial reports

Provide full clinical trial reports where clinical data are required, unless providing a literature based submission.

Present clinical data as specified in the following CTD modules:

- Modules 2.5 *Clinical Overview* - provides a critical analysis of the clinical data in the dossier
- Module 2.7 *Clinical Summary* - provides a detailed, factual summary of all of the clinical information provided
- Module 5 Clinical Study Reports.

Good clinical practice

Ensure that all phases of clinical investigation are conducted in accordance with Good Clinical Practice (GCP) guidelines. You will need to include a statement regarding GCP compliance in the Clinical Overview (Module 2.5 of the CTD).

Clinical trials information and guidance

We have adopted a large number of European Union (EU) clinical guidelines, some with annotations. Some key clinical guidelines adopted include:

- *Note for Guidance on Coordinating Investigator Signature of Clinical Study Reports* (CPMP/EWP/2747/00)
- *Note for Guidance on Structure and Content of Clinical Study Reports* (CPMP/ICH/137/95)
- *Note for Guidance on General Considerations for Clinical Trials* (CPMP/ICH/291/95)
- *Note for Guidance on Statistical Principles for Clinical Trials* (CPMP/ICH/363/96)
- *Note for Guidance on Choice of Control Groups in Clinical Trials* (CPMP/ICH/364/96)
- *Note for guidance on clinical requirements for locally applied, locally acting products containing known constituents* (CPMP/EWP/239/95 final)

Other clinical EU guidelines adopted in Australia that pertain to specific medicines, clinical aspects or study methodology may also be relevant to your application.

4.3 Non-clinical studies

Provide non-clinical studies for any of the following unless otherwise justified:

- medicines with new ingredients (actives or excipients)
- new fixed dose combinations
- new routes of administration for an ingredient
- higher doses of active or excipient ingredients, or use over a longer period of time, than currently approved. Contact OTC Medicines if you are unsure
- medicines with impurity limits that are above those allowed without justification in the Guidelines on quality aspects of OTC Medicines.

Where there is a substantial history of use in comparable regulatory jurisdictions (e.g. UK, Canada, US), we may accept a justification based on safety-in-use substantiation from post-market information in place of non-clinical data.

Related information and guidance

ARGOM Appendix 4: Guidelines on OTC applications for new substances

4.4 Post-market information

Post-market information may provide further support for safety where aspects of the medicine are new to the Australian market but have been available for some time overseas. Examples may include applications for new:

- active ingredients
- fixed dose combinations
- proposed indications
- directions for use.

Where appropriate, include relevant post-market information as follows:

- details of adverse medicine reaction reports from Australia and/or from relevant authorities in countries with similar regulatory systems to Australia
- copies of relevant 'Periodic safety update reports' (PSURs).

5 - Legislative basis for safety and efficacy data

5.1 Registering a new medicine in the ARTG

Applications to register a medicine in the ARTG (made under section 23 of the Act) must be evaluated to confirm whether the **quality**, **safety** and **efficacy** of the goods (for the purposes they are intended to be used for) have been satisfactorily established (see subsection 25(1) of the Act).

5.2 Varying a medicine included in the ARTG

These applications (made under section 9D(3) of the Act) are evaluated to ensure that the variation which has been requested does not show any reduction in the **quality**, **safety** and **efficacy** of the goods for the purposes they are intended to be used for.

Version history

Version	Description of change	Author	Effective date
V1.0	Update of ARGOM Chapter 6A Efficacy and safety Re-formatting of Chapter 6A as Appendix 1 - Guidelines on efficacy and safety aspects of OTC applications.	MAG – OTCME	October 2012
V2.0	Webpage format and changed structure Moved definition of 'generic' to a standalone web page Updated 'Standard reference texts' and moved to section 4 'Types of data' Updated LBS guidance and linked to common TGA guidance Revised 'bioequivalence data' Added cases where bioequivalence data not required Included ingredients which do not need bio data under 'Bioequivalence' Included reference to generic combination medicines Requirements for justification of biowaiver links to ARGPM Guidance 15 Updated 'Therapeutic equivalence data' for topicals Added list of topical generics for which therapeutic equivalence data are not required Revised 'Products with a new dosage form' section Reworded Fixed combination guidance Replaced Modified release guidance with reference to adopted EU guidance	OTC Medicines Regulatory Guidance	30 November 2015

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