



Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian regulatory guideline for over-the-counter medicines

Appendix 1: Guidelines on efficacy and safety aspects of OTC applications

Version 1.0, October 2012

TGA Health Safety
Regulation



Historical document

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>.

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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

Historical document

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Introduction

The *Therapeutic Goods Act 1989*¹ (the Act) requires that applications for a product 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*”.

All applications for over-the-counter (OTC) medicine registration must be supported by evidence to substantiate the safety and efficacy of the product. This part of the guidance document describes the types of evidence that should be submitted for the various OTC medicine applications. It is divided into eleven sections as follows:

1. [Standard reference texts](#)
2. [Literature-based submissions](#)
3. [Clinical trials on the proposed products](#)
4. [Preclinical studies](#)
5. [Post market experience](#)
6. [‘Generic’ products](#)
7. [Product specific requirements](#)
8. [Products with a ‘new’ dosage form](#)
9. [Fixed combination products](#)
10. [Modified release products](#)
11. [Active ingredients for which bioequivalence data are generally not required](#)

In some cases, where safety and efficacy of the proposed product are well established in Australia and bioequivalence data are not required, provision of supporting evidence to the TGA may not be necessary (see [‘section 6.1 Bioequivalence data’](#)). Deviations from these guidelines may be accepted provided sound justification is given.

¹ <http://www.tga.gov.au/industry/legislation.htm>

1. Standard reference texts

For some OTC medicine applications, evidence to support safety and efficacy may be found in standard reference texts. Where this is the case, further information on the safety and efficacy of the product may not be required.

Applications based on standard reference texts should include an overview or covering letter referring to the texts and detailing their relevance (copies of the relevant pages should be provided).

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:

- Handbook of Non-prescription Drugs, American Pharmacists Association, USA
- Martindale: The Complete Drug Reference, Sweetman SC (Ed.), Pharmaceutical Press, UK
- Remington: The Science and Practice of Pharmacy, Gennaro AR (Ed.), Lippincott Williams & Wilkins, USA
- Handbook of Pharmaceutical Excipients, Kibbe AH (Ed.) American Pharmacists Association, USA and Pharmaceutical Press, UK
- AHFS Drug Information, McEvoy GK (Ed.), American Society of Health System Pharmacists, USA
- Meyler's side effects of drugs; Dukes MNG et al. (Eds), Elsevier

Current editions should be referenced unless otherwise justified. Note that limited clinical reports of efficacy alone or anecdotal reports (e.g. in Martindale "xxx has also been used in ...") are not regarded as adequate evidence of safety and efficacy.

Reference texts alone will **not** usually be sufficient to establish safety and efficacy in the following circumstances:

- for 'new' active ingredients (i.e. not currently an active ingredient in any medicine on the Australian Register of Therapeutic Goods (ARTG));
- where bioequivalence data are required (see '[Section 6.1 Bioequivalence data](#)')
- where therapeutic equivalence data are required for topical medicines (see '[Section 6.2 Therapeutic equivalence data – topical products](#)');
- where the medicine is a nasal spray/aerosol containing a corticosteroid (see '[Section 7.1 Nasal corticosteroid sprays/aerosols](#)');
- where the medicine is in a metered dose inhaler form (see '[Section 7.4 Metered-dose inhalers](#)');
- where the medicine is in a new dosage form compared to other medicines on the ARTG with the same active ingredient (see '[Section 8 Products with a 'new' dosage form](#)');
- where the medicine contains a 'new' fixed dose combination of active ingredients (see '[Section 9 Fixed combination products](#)');
- where the medicine is in a modified release dosage form (see '[Section 10 Modified release products](#)'); and
- where the medicine has a route of administration that has not been used before for medicines on the ARTG with the same active ingredient

2. Literature-based submissions

In circumstances where the sponsor lacks supportive data of their own but considers available published scientific literature to be supportive, it may be appropriate to submit a 'literature-based submission'. This option may be appropriate for applications such as changes to indications or directions for use or less commonly for new product applications. The supporting literature must be appropriately relevant to the application – for example the information should generally relate closely to the formulation, dosage regimen and indications of the proposed product.

A literature-based 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*². For older medicines or where relevant reports are few, the search may need to include all records in *Medline* and/or other databases such as *Embase*³. To enable critical analysis or duplication of the search by the TGA, details of the search strategy and search output should be included (electronically on CD/DVD, as well as hard copy) in the application. The search output should be annotated to include those papers selected for inclusion in the submission and cross-referenced to the overview. A list or table of reports which have been excluded from consideration should be presented together with reasons for exclusion. All submitted data/papers etc. should be page numbered.

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

- the trials are conducted using the same active ingredient(s) with the same dosage concentration, a similar dosage regimen, dosage form, route of administration and indications 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 safety and efficacy of the product proposed for registration.

Trials should be excluded if they are not consistent with the above, or if they are poorly conducted or reported, or not of sufficient power to produce statistically significant results. All relevant, well-conducted and reported trials should be included regardless of whether the findings are adverse to the product proposed for registration. For relevant trials which are reported in a language other than English, a certified translation should be provided.

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

2.1 Overview and summary of reports

A literature-based submission must include an overview, which includes a **critical appraisal of all the papers submitted**. In the Common Technical Document (CTD) format⁴ this overview effectively forms module 2.5 for clinical data (in the "old European format" this overview would include the expert report).

The overview should include the reasons for selecting and excluding retrieved published papers and refer to the selection criteria used. Issues such as publication bias and

² http://www.nlm.nih.gov/databases/databases_medline.html

³ <http://www.embase.com/info/what-is-embase>

⁴ <http://www.tga.gov.au/industry/pm-ctd.htm>

potential duplication of data from the same subjects in different papers should be discussed where relevant.

The overview should also include a comprehensive appraisal of the quality of all the papers submitted, the quality of the clinical trials reported in those papers, and the quality of the data generated. Studies considered to be pivotal should be identified and a rationale provided. Data from randomised, double blind, controlled studies would be expected to be given greater weight than data from non-randomised, uncontrolled or open studies. The papers need to be discussed individually and collectively in terms of the weight of evidence they provide. Implications of any differences in formulation used in the literature reports should be discussed.

A table should also be included giving 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 study or report (e.g. double blind, randomised, multi-centre, cross-over trial);
- the number of subjects included in the trial;
- treatment details, including details of the dosage form, formulation, dosage schedule and treatment duration;
- parameters studied; and
- summary of results in relation to efficacy and safety.

With regard to safety data, there should be tabulation and analysis of all adverse events (including abnormal laboratory values, medicine interactions etc.) for all documented clinical studies and any adverse events which have been reported to the sponsor. Further guidance on literature-based submissions may be found on the TGA website⁵.

3. Clinical trials on the proposed product

In circumstances where safety and efficacy data are required but neither standard references nor a literature-based submission are appropriate, it will be necessary to provide reports of clinical trials that the sponsor has conducted to establish the safety and efficacy of the product proposed for registration.

Clinical data should preferably be presented as specified in Modules 2.5 *Clinical Overview*, 2.7 *Clinical Summary* and Module 5 *Clinical Study Reports* of the CTD format⁶. The clinical overview is intended to provide a critical analysis of the clinical data in the dossier while the clinical summary is intended to provide a detailed, factual summarisation of all of the clinical information provided.

The following relevant European Guidelines developed by the Committee for Medicinal Products for Human Use (CPMP) have been adopted by the TGA (with annotations) and can be found on the TGA website⁷.

⁵ <http://www.tga.gov.au/industry/pm-literature-based-submissions.htm>

⁶ <http://www.tga.gov.au/industry/pm-ctd.htm>

⁷ <http://www.tga.gov.au/industry/pm-euguidelines-adopted-clinical.htm>

- *Note for Guidance on Coordinating Investigator Signature of Clinical Study Reports* (CPMP/EWP/2747/00)
- *Note for Guidance on Good Clinical Practice – annotated with TGA comments* (CPMP/ICH/135/95)
- *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)
- *Clinical Overview, Clinical Summary of Module 2 and Module 5: Clinical Study Reports* (CPMP/ICH/2887/99/Rev 1 Efficacy)
- *Guideline on the Investigation of Bioequivalence* (CPMP/EWP/QWP/1401/98 Rev 1)(adopted by TGA with additional notation)
- *Clinical requirements for locally applied, locally acting products containing known constituents* (pp. 193 - 198 of Rules 1998 (3C) - 3CC12a)
- *General Questions and Answers. Common technical document for the registration of pharmaceuticals for human use* (CPMP/ICH/5552/02)

Other CPMP guidelines may be relevant to particular applications. Details of all CPMP guidelines adopted by the TGA can be found on the TGA website⁸.

3.1 Good clinical practice (GCP)

The TGA requires that all phases of clinical investigation be conducted in accordance with acceptable guidelines for Good Clinical Practice (GCP). The *Note for Guidance on Good Clinical Practice* (CPMP/ICH/135/95 – Annotated with TGA comments)⁹ should be referred to. A statement regarding GCP compliance should be included in the Clinical Overview (Module 2.5 of the CTD format¹⁰) or the study report.

3.2 Ethical certification

The *Note for Guidance on Good Clinical Practice* (CPMP/ICH/135/95 – Annotated with TGA Comments)¹¹ states that "Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s)." For trials conducted in Australia applicable regulatory requirements include the National Health and Medical Research Council (NHMRC) *National Statement on Ethical Conduct in Research Involving Humans*¹². The sponsor must be able to provide the TGA with any relevant documentation, including approval letters from Human Research Ethics Committees (HRECs), specimen subject consent forms and patient information sheets if requested.

⁸ <http://www.tga.gov.au/industry/pm-euguidelines-adopted.htm>

⁹ <http://www.tga.gov.au/industry/pm-euguidelines-adopted-clinical.htm#clinicalgeneral>

¹⁰ <http://www.tga.gov.au/industry/pm-ctd.htm>

¹¹ <http://www.tga.gov.au/industry/pm-euguidelines-adopted-clinical.htm#clinicalgeneral>

¹² <http://www.nhmrc.gov.au/node/1278>

4. Preclinical studies

In most cases, OTC medicines have a substantial history of use in humans, reports of trials in animals are usually not required. However, for products with 'new' ingredients, new fixed dose combinations, new routes of administration, higher than normally accepted dosages or for use over a longer period of time, animal trial data will be required unless otherwise justified (see also *ARGOM Appendix 4 Guideline on OTC applications for new substances*¹³). Where there is a substantial history of use in comparable regulatory jurisdictions (e.g. UK, Canada, US) it may be acceptable to provide a safety in use substantiation from post market surveillance data as an alternative to preclinical studies; (see '[Section 5 Post-market experience](#)').

5. Post-market experience

In some circumstances it may be appropriate to include details of adverse medicine reaction reports from Australia and/or from relevant authorities in countries with similar regulatory systems to Australia. Copies of 'Periodic safety update reports' (PSUR's) may also be relevant. Examples of circumstances where such information may be necessary include where active ingredients, fixed dose combinations, proposed indications or directions for use are new to the Australian market but have been marketed overseas.

6. 'Generic' products

An 'originator' product (sometimes referred to as the 'innovator' product) is a medicine that has been approved for marketing in Australia on the basis of a full dossier which may include chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. A 'generic' product is a medicine that, in comparison to the originator product:

- has the same quantitative composition of therapeutically active substances, being substances of similar quality to those in the originator product; and
- has the same pharmaceutical form; and
- is bioequivalent (or for topical products, is considered to be therapeutically equivalent – see '[Section 6.2 Therapeutic equivalence data - topical products](#)'); and
- have the same safety and efficacy properties.

Regarding point 2 above, the various immediate-release oral dosage forms (e.g. tablets, capsules, oral liquids or suspensions) can be considered to be one and the same pharmaceutical form (see '[Section 8 Products with a 'new' dosage form](#)').

The TGA will accept applications to register 'generic' products without further safety and efficacy data where the proposed indications and dosage regimen are the same as those of the originator product and where the safety and efficacy data provided with the originator product are not 'protected' (Section 25A of the *Therapeutic Goods Act 1989* refers¹⁴). In some cases however, data will be required to demonstrate that the proposed 'generic' is bioequivalent to the originator product (i.e. that it qualifies as a 'generic'; see '[Section 6.1](#)

¹³ <http://www.tga.gov.au/industry/otc-argom-app4.htm>

¹⁴ <http://www.tga.gov.au/industry/legislation.htm>

[Bioequivalence data](#)'). For some proposed topical products, where the formulation may have a significant impact on efficacy and/or safety, data may be required to establish therapeutic equivalence with the originator product (see '[Section 6.2 Therapeutic equivalence data – topical products](#)').

Where bioequivalence [or therapeutic equivalence for a topical product – see '[Section 6.2 Therapeutic equivalence data - topical products](#)'] is a requirement, a generic medicine must be shown to be bioequivalent (or therapeutically equivalent) to the corresponding strength of a leading brand (normally the originator product) as marketed in Australia. However, in some circumstances the TGA may accept bioequivalence (or therapeutic equivalence) studies carried out using samples of the originator product obtained from outside Australia, provided the sponsor can support this with evidence that the formulation of this product is the same as the formulation marketed in Australia. Details of the evidence required for oral products in this case can be found in the *Australian Regulatory Guidelines for Prescription Medicines (ARGPM) - Appendix 15 Biopharmaceutic Studies*¹⁵.

6.1 Bioequivalence data

Detailed information on TGA requirements for biopharmaceutic studies can be found in the *Australian Regulatory Guidelines for Prescription Medicines (ARGPM) – Appendix 15 Biopharmaceutic Studies*¹⁶ and the European Union (EU) guideline, *Guideline on the investigation of bioequivalence* (CPMP/EWP/QWP/1401/98 Rev 1)¹⁷, which has been adopted by the TGA with annotations.

In most cases, bioequivalence data are not required for OTC medicines, but for some products, particularly those containing more recently approved or down-scheduled active ingredients, bioequivalence data may be required.

Bioequivalence data, or a justification for not providing bioequivalence data, are generally required for oral 'generic' products **except** in the following circumstances:

- where there are other oral 'generic' products on the register that have been approved without either bioequivalence data (not including clones of the originator product) or a justification for not providing bioequivalence data. A large number of OTC products will fall into this category - see '[Section 11 Active ingredients for which bioequivalence data are generally not required](#)' or contact the TGA if unsure;
- products that are aqueous oral solutions at the time of administration and contain an active substance in the same concentration as an oral solution currently approved as a medicinal product, provided the excipients contained in them do not affect gastrointestinal transit, absorption or in vivo stability of the active substance, for example gastric pH changes; or
- products which contain active ingredients that are not absorbed (e.g. barium sulphate, simethicone, alginic acid).

For OTC 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, bioequivalence data will not be required if an acceptable

¹⁵ <http://www.tga.gov.au/industry/pm-argpm.htm>

¹⁶ <http://www.tga.gov.au/industry/pm-argpm.htm>

¹⁷ <http://www.tga.gov.au/industry/pm-euguidelines-adopted-clinical.htm>

justification for not providing such data can be provided (see also '[Section 8 Products with a new dosage form](#)').

Justifications for not providing bioequivalence data should address at least the following issues where applicable:

- the nature of the dosage form
- the solubility of the active ingredient(s)
- the comparative dissolution profiles across the physiological pH range (1-7.5) of the products being considered
- the pharmacokinetic characteristics of the active ingredient(s), such as permeability (or absolute bioavailability), linearity or otherwise, first pass effect (if any) and its significance
- the clinical consequences of any potential differences in bioavailabilities of the products under consideration (e.g. increased dose leading to toxicity or decreased dose leading to lack of efficacy)
- the width of the margin between the minimum effective and minimum toxic plasma concentrations
- the similarities of, or differences between, the formulations being considered.

More details regarding justifications for not providing bioequivalence data can be found in *Guideline on the investigation of bioequivalence* (CPMP/EWF/QWP/1401/98 Rev 1): Section 5.1, which has been adopted by the TGA with annotations, and as outlined in *ARGPM Appendix 15 Biopharmaceutic Studies*¹⁸

Copies of any cited literature should be provided. If the justification is considered inadequate by the TGA, the sponsor will be required to provide bioequivalence or other clinical data for the application to proceed.

To assist the evaluator(s) in identifying the studies to be assessed and locating the relevant information, sponsors submitting biopharmaceutic data are strongly encouraged to complete, for each study, the optional *Summary of a Bioavailability or Bioequivalence Study* form¹⁹. For applications submitted in CTD format²⁰, completed summary forms should be included as part of Module 1.

Products for topical use intended to act without systemic absorption do not generally require bioequivalence data (i.e. using systemic measurements), but therapeutic equivalence data may be required – see Section 6.2 'Therapeutic equivalence data - topical products'.

6.2 Therapeutic equivalence data - topical products

Some topical OTC medicines have a long history of use in many different formulations and their efficacy is well accepted (e.g. salicylic acid for treatment of warts). Efficacy and safety data are generally not required to support the registration of such generic products.

¹⁸ <http://www.tga.gov.au/industry/pm-argpm.htm>

¹⁹ <http://www.tga.gov.au/industry/pm-forms-bioavailability.htm>

²⁰ <http://www.tga.gov.au/industry/pm-ctd.htm>

Where the efficacy of the product is likely to be formulation dependent (see below for examples), the efficacy of the particular formulation proposed for registration will need to be established.

The TGA has identified certain topical products where the efficacy and/or safety of the product are influenced by the formulation. In these cases, differences in non-active ingredients may affect the extent of penetration of the active substance and therefore efficacy and/or safety data are usually required before the product is approved for registration. As OTC medicines are so diverse, the TGA has adopted a flexible approach in which the need for data to support registration of generic topical products should be determined on a case-by-case basis.

The following ingredients or product categories have been identified as being formulation dependent in terms of efficacy and/or safety:

- Head lice preparations
- Aciclovir for treatment of cold sores
- Minoxidil
- NSAIDs
- Antiseptics/skin disinfectants [See *ARGOM Appendix 6 Antiseptics/skin disinfectants* (still to be finalised)]
Note: Antiseptics guideline is under a review at the TGA.
- Antidandruff shampoos containing imidazole antifungals as active ingredients
- Dithranol preparations
- Corticosteroids (except hydrocortisone) (see '[Section 7.1 Nasal corticosteroid sprays](#)')
- Products containing glyceryl trinitrate (see '[Section 7.5 Oral nitrate products](#)')

The above list is not exhaustive and the absence of any ingredient does not necessarily indicate that safety or efficacy are considered to be independent of formulation – the ingredient may simply not have been considered by the TGA in this regard (e.g. for recently down-scheduled ingredients). The TGA will endeavour to update the list as new categories are identified as being formulation dependent.

In some cases the TGA may seek advice from the Advisory Committee on Non-prescription Medicines (ACNM) regarding data requirements for a particular product (e.g. for topical products containing active ingredients that have been down-scheduled from prescription to OTC). In most instances, the ACNM has advised that data from clinical trials would be required to support the application of formulation-dependent topical products.

For guidance on data requirements for locally applied/acting products, refer to the EU document *Clinical requirements for locally applied, locally acting products containing known constituents* (pp. 193 - 198 of Rules 1998 (3C) - 3CC12a)²¹.

²¹ <http://www.tga.gov.au/industry/pm-euguidelines-adopted-clinical.htm>

7. Product specific requirements

7.1 Nasal corticosteroid sprays/aerosols

Given the specialised clinical and quality data requirements for registration of these products, applications for registration of these products have routinely been referred to the prescription medicines evaluation area for evaluation. Such applications should be submitted to the *Office of Medicines Authorisation of prescription and other medicines* in accordance with the *Australian Regulatory Guidelines for Prescription Medicines (ARGPM)*. The safety and efficacy data required to support the registration of OTC corticosteroid nasal sprays/aerosols are as indicated in the *ARGPM Appendix 19 Metered dose aerosols (pressurised and non-pressurised)*²².

7.2 Nicotine replacement therapy products

The safety and efficacy data requirements for nicotine replacement therapy (NRT) products are included in *ARGOM Appendix 5 Guidelines on OTC applications: Nicotine replacement therapy*²³. Applications for new transdermal NRT products should be submitted to the *Office of Medicines Authorisation of prescription and other medicines* in accordance with the *Australian Regulatory Guidelines for Prescription Medicines (ARGPM)*, in accordance with Part 1 of Schedule 10 of the *Therapeutic Goods Regulations 1990*²⁴ (the Regulations).

7.3 Antiseptics/skin disinfectants

The safety and efficacy data requirements for antiseptics and skin disinfectants are specified in the *ARGOM Appendix 6 Antiseptics/skin disinfectants* [still to be finalised].

7.4 Metered-dose inhalers

Given the specialised clinical and quality data requirements for registration of these products, applications for registration of these products have routinely been referred to the prescription medicines evaluation area for evaluation. Such applications should be submitted to the *Office of Medicines Authorisation of prescription and other medicines* in accordance with the *Australian Regulatory Guidelines for Prescription Medicines (ARGPM)*. The safety and efficacy data required to support the registration of OTC metered dose inhalers for use in asthma are as indicated in the *ARGPM Appendix 19 Metered dose aerosols (pressurised and non-pressurised)*²⁵.

²² <http://www.tga.gov.au/industry/pm-argpm.htm>

²³ <http://www.tga.gov.au/industry/otc-argom-app5.htm>

²⁴ <http://www.tga.gov.au/industry/legislation.htm>

²⁵ <http://www.tga.gov.au/industry/pm-argpm.htm>

7.5 Oral nitrate products

Given the specialised clinical and quality data requirements for registration of these products and the serious nature of the conditions being treated, applications for registration of these products have routinely been referred to the prescription medicines evaluation area for evaluation. Such applications should be submitted to the *Office of Medicines Authorisation of prescription and other medicines* in accordance with the *Australian Regulatory Guidelines for Prescription Medicines* (ARGPM).

8. Products with a 'new' dosage form

Applications for products containing active ingredients that have not previously been included in the proposed dosage form will generally require full clinical data. However, where the originator and new product are both immediate release oral dosage forms (e.g. a tablet, capsule, oral liquid or suspension), the TGA will accept applications to register the 'new' product without clinical data on the basis of data that demonstrate that the 'new' and 'originator' products are bioequivalent, or a justification that bioequivalence data are not required (refer to '[Section 6.1 Bioequivalence data](#)' above), provided the following apply:

- there is no reason to consider that safety and efficacy properties would differ; and
- the indications and dosage regimen are the same as those of the 'originator' product; and
- the clinical data provided with the 'originator' product are not 'protected' (Section 25A of the Act refers²⁶).

Where a 'new' dosage form has sustained release characteristics, the guideline as set out in Section 10 'Modified release products' should be followed.

9. Fixed combination products

The data requirements for supporting registration of fixed combination products are as described in the *Guideline on Clinical Development of Fixed Combination Medicinal Products* (CPMP/EWP/240/95 Rev1)²⁷, which has been adopted by the TGA. An outline of requirements and issues to consider is included below, but the guideline should be consulted for full requirements. In general, data requirements for new composite packs containing multiple active ingredients are the same as those for fixed combination products.

The particular combination of active ingredients in a proposed new combination product must be justified. Each active ingredient must make a therapeutic contribution to the claimed indications and the product must provide rational concurrent therapy for a significant proportion of the target population. Where individual substances in the combination are intended simultaneously to relieve different symptoms of a particular disease state, these symptoms should regularly occur simultaneously in a clinically

²⁶ <http://www.tga.gov.au/industry/legislation.htm>

²⁷ <http://www.tga.gov.au/industry/pm-euguidelines-adopted-clinical.htm>

relevant intensity and for a relevant period of time. The dose and proportion of each active ingredient must also be appropriate for the intended use.

The safety and efficacy of the combination will need to be supported. The possibility of pharmacodynamic and pharmacokinetic interactions between the active ingredients must be considered. Clinical efficacy and pharmacokinetic data comparing the proposed product with the active ingredients used separately will usually be required. Refer to the above CPMP document for detailed guidance.

If an oral combination product is proposed as a generic of an existing combination product, then safety or efficacy data should not be required, except that bioequivalence data may be required. The requirements for bioequivalence data are the same as those that would apply for each active ingredient individually, as if they were the sole active ingredient (see '[Section 6.1 Bioequivalence data](#)'). For example, bioequivalence data should not be required for a particular component active ingredient where, based on its inclusion in '[Section 11 Active ingredients for which bioequivalence data are not generally required](#)', bioequivalence data would not be required if it was the sole active ingredient.

Where one or more component ingredients have modified-release characteristics, the guideline on modified-release products also applies.

10. Modified release products

Modified release oral dosage forms (as defined in the *Therapeutic Goods Order (TGO) 78 Standard for tablets and capsules*²⁸) may be appropriate where:

- the active ingredient has rapid absorption and elimination (e.g. 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' does not 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).

²⁸ <http://www.tga.gov.au/industry/legislation-tgo.htm>

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.

Where it is believed that a particular application warrants a departure from this guideline, a full justification for the departure should be submitted with the application. If the justification is not accepted, studies as above will be required.

Further information on data requirements can be found in the CPMP guideline document *Note for guidance on modified release and transdermal dosage forms: Section II (Pharmacokinetics and Clinical Evaluation)* (CPMP/EWP/280/96)²⁹.

11. Active ingredients for which bioequivalence data are generally not required

Applications to register immediate-release oral dose form (e.g. tablet, capsule, oral liquid or suspension) 'generic' products that contain active ingredients included in the list below would not usually require provision of bioequivalence data or a justification for not providing such data.

The below list has been determined in accordance with the guidelines detailed in '[Section 6.1 Bioequivalence data](#)'.

- Aspirin
- Bromhexine hydrochloride
- Brompheniramine maleate
- Chlorpheniramine maleate
- Codeine phosphate
- Dexchlorpheniramine maleate
- Dextrometorphan hydrobromide
- Dimenhydrinate
- Diphenhydramine hydrochloride
- Eucusate sodium
- Doxylamine succinate
- Guaiphenesin
- Hyoscine hydrobromide
- Hyoscine butylbromide
- Ibuprofen
- Loperamide hydrochloride
- Mebendazole

²⁹ <http://www.tga.gov.au/industry/pm-euguidelines-adopted-clinical.htm>

- Naproxen
- Naproxen sodium
- Paracetamol
- Phenylephrine hydrochloride
- Promethazine hydrochloride
- Pseudoephedrine hydrochloride
- Ranitidine hydrochloride
- Triprolidine hydrochloride

If, however, there is reason to consider that bioavailability of a proposed product might differ from existing products so as to impact on efficacy and/or safety (e.g. proposed novel dose form), bioequivalence data or a justification for not providing such data may be required despite inclusion of the relevant ingredient in the list. Further, where a proposed product is not a 'generic' of an existing product (e.g. a new combination product or strength), bioequivalence or other clinical data, or a justification for not providing such data, would be required despite inclusion of the relevant ingredient in the list.

Historical document

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Reference/Publication #