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**Department of Health**

Therapeutic Goods Administration

# Assessed listed medicines evidence guidelines

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**TGA** Health Safety  
Regulation

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# Contents

<b>1. Overview</b>	<b>6</b>
Risk-based classification	6
Benefits of the assessed listed medicines pathway	6
<b>2. Eligibility and regulatory requirements</b>	<b>8</b>
2.1 General requirements	8
2.2 Evidence of GMP	9
2.3 Indications and presentation	9
<b>3. Indications</b>	<b>11</b>
3.1 Risk categorisation	11
3.2 How to structure an indication	12
3.3 Indications for assessed listed medicines	14
<b>4. Application categories</b>	<b>18</b>
4.1 Application category: L(A)1	18
4.2 Application category: L(A)2	20
4.3 Application category: L(A)3	20
4.4 Variations to an existing assessed listed medicine	21
<b>5. Evidence requirements and standards</b>	<b>22</b>
5.1 Methods of establishing efficacy	22
5.2 Types of applications	25
5.3 Literature search report	25
5.4 Standards of evidence	26
5.5 Biopharmaceutic and pharmacokinetic studies	43
5.6 Justifications	47
<b>6. Alignment of indications and evidence</b>	<b>48</b>
6.1 Formulation and use	48
6.2 Duration of studies	49
6.3 Outcomes	49
6.4 Context	49
6.5 Target population and generalisation/extrapolation	50
6.6 Balance of evidence	51

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<b>7. Presentation</b>	<b>52</b>
7.1 Unacceptable presentation	52
7.2 Name	53
7.3 Labels	54
7.4 Advertising	57
<b>8. Application dossier requirements</b>	<b>58</b>
<b>9. Application and approval processes</b>	<b>59</b>
9.1 Pre-submission	59
9.2 Application submission	61
9.3 Preliminary assessment	62
9.4 Evaluation and requests for information	62
9.5 The decision	63
9.6 Finalisation	64
9.7 Post-listing	64
<b>10. Timeframes and fees</b>	<b>66</b>
Timeframes	66
Fees	66



The assessed listed medicines pathway, established following the Government's acceptance of Recommendation 39 of the [Medicines and Medical Devices Regulation review](#), provides sponsors with a new method of listing a product in the Australian Register of Therapeutic Goods (ARTG). The new pathway sits between the current listed (lower risk) and registered (higher risk) pathways. It enables sponsors to list products with higher level indications than permitted in standard listed medicines without having to meet the extensive requirements for full registration. This is provided that assessed listed medicines have robust scientific evidence to support the efficacy of the product, and this evidence is pre-market assessed by the TGA.

This guidance applies to 'assessed listed medicines' that are eligible for evaluation by the TGA's Complementary and Over-the-counter Medicines Branch (COMB). As this is a new pathway, we will continue to refine this guidance as necessary.

# 1. Overview

There are three types of complementary medicines available to consumers: listed medicines, assessed listed medicines and registered complementary medicines. These are categorised on the ingredients they contain and therapeutic indications they use. **Assessed listed medicines** are products that meet the eligibility criteria for listed medicines but which use indications that, while still appropriate for listed medicines, fall outside the [list of Permitted Indications](#).

The products can only be listed in the ARTG following self-certification by the applicant of the safety and quality of the product, and **pre-market assessment** by the TGA of the efficacy evidence supporting the proposed indications and claims. Medicines that have undergone pre-market assessment and approval by the TGA have a unique AUST L(A) number, and may carry a claim that the product's efficacy has been assessed for the approved indications (this is currently under development).

There are three application categories for assessed listed medicines which have different evidence requirements depending on the level of efficacy evaluation (see [Application Categories](#)). This document provides guidance for the evidence requirements for all application categories, however a majority is dedicated to L(A)3 applications as these products require a *de novo* evaluation of efficacy.

## Risk-based classification

Like all listed medicines, assessed listed medicines may only contain low risk ingredients specified in the [Therapeutic Goods \(Permissible Ingredients\) Determination](#) and must be produced under [Good Manufacturing Practice \(GMP\)](#) principles. The safety and quality of the finished products are self-certified by the applicant and are not pre-market assessed by the TGA.

Assessed listed medicines may make indications that fall outside the list of permitted indications but which are not of a type necessitating registration of the product. These 'intermediate level' indications are generally more definitive than indications on listed medicines; relate to more serious health conditions; and may lead to a delay in seeking medical treatment and/or adverse consequences for the consumer if the product is used incorrectly or is not efficacious (see [Indications](#)).

Therefore, while assessed listed medicines are considered to be low risk based on their ingredients, manufacture, and route of administration, they are considered to be of higher risk than listed medicines based on the therapeutic indications they carry. Assessed listed medicines are consequently subject to a pre-market evaluation by the TGA of the scientific evidence supporting the proposed indications before the product can be listed in the ARTG.

Only products supported by high quality **scientific evidence** can be accepted for assessment through the assessed listed medicines pathway. Products that have indications supported **solely** by animal studies, tradition of use, or anecdotal data will not be accepted.

If the TGA determines that the efficacy of the proposed product is well supported by evidence and the product meets all other requirements for listed medicines, it can be listed in the ARTG.

## Benefits of the assessed listed medicines pathway

The assessed listed medicines pathway bridges a significant gap that exists between the evidence requirements, costs, and timeframes for the listed and registered medicines pathways. It provides flexibility for sponsors to access higher level indications than are currently appropriate for listed medicines, without mandating data requirements that are not commensurate with the risks. This pathway provides a market advantage to sponsors via higher

level indications and a claim on labels and promotional materials; supports innovation; and encourages an expansion of the evidence base for complementary medicines.

The assessed listed medicines pathway provides significant benefits to consumers and health professionals - increasing the transparency of the evidence base for claims; improving confidence in products; enabling consumers to make more informed healthcare decisions; and facilitating greater consumer access to a wider range of evidence-based remedies to self-manage their health.

## 2. Eligibility and regulatory requirements

In order for applicants to utilise the assessed listed medicines pathway, the proposed product must meet all the safety and quality requirements for listed medicines. Additionally, assessed listed medicines must meet specific requirements relating to efficacy, presentation and supporting evidence.

Applicants must certify that the proposed product meets the requirements of subsection 26AB(2) of the *Therapeutic Goods Act 1989* (the Act), and if applicable, subsection 26AB(3). Part B of the [Australian Regulatory Guidelines for Complementary Medicines \(ARGCM\)](#) provides detailed information on the safety, quality and efficacy statutory requirements and conditions for listed medicines. The ARGCM will be updated to include the requirements and conditions for assessed listed medicines. In the meantime, applicants may refer to the requirements for listed medicines in Part B of ARGCM for general information; the requirements for assessed listed complementary medicines are similar, except with respect to the pre-market assessment of the efficacy evidence by the TGA.

Key elements of the assessed listed requirements are summarised below.

### 2.1 General requirements

Medicines listed via the assessed listed medicines pathway must:

- contain only permitted ingredients that have been evaluated for safety and quality, and meet the requirements associated with their use in listed medicines. These ingredients and their associated requirements are specified in the [Therapeutic Goods \(Permissible Ingredients\) Determination](#);
- not contain ingredients included in a schedule to the [Standard for the Uniform Scheduling of Medicines and Poisons \(SUSMP\)](#);
- not be required to be sterile. Consistent with the current listing framework, a medicine that is required to be sterile cannot be listed via the AUST L(A) pathway (see Schedule 4 of the *Therapeutic Goods Regulations 1990*);
- not be a prohibited import for the purposes of the [Customs Act 1901](#);
- meet all specifications for the shelf life of the medicine, the recommended storage conditions and the expiry date stated on the product label;
- comply with all [applicable standards](#) and legislative requirements in relation to quality and safety of medicines;
- not be an export only medicine; and
- not be a medicine that has previously had its registration or listing cancelled.

The sponsor must self-assess and certify under subsection 26AB(2) of the Act that the medicine meets the above requirements. These aspects of the medicine are not pre-market assessed by the TGA, but may be subsequently reviewed during standard post-market compliance processes. If the medicine exceeds some of the above requirements (e.g. ingredients not in the Permissible Ingredients determination), then it may be suitable for the registered pathway.

## 2.2 Evidence of GMP

Assessed listed medicines must be produced in accordance with the PIC/S Guide to GMP (see [Manufacturing principles for medicinal products](#)).

Applicants must provide valid evidence that the manufacturer(s) of the product have applied GMP for each step of manufacture. This evidence is:

- a copy of a GMP licence issued by the TGA (for Australian manufacturers)
- a GMP clearance issued by the TGA (for overseas manufacturers)

Applicants must also ensure that the GMP clearance remains valid for the entire duration of the evaluation from the date of submission. The [target timeframes](#) vary for different [application categories](#). If the GMP clearance is due to expire within the minimum timeframe or is likely to expire before the application is finalised, applicants should either apply to renew the GMP clearance or seek an extension to the GMP clearance expiry before submitting the application.

For further information refer to [Guidance on manufacturing medicines](#) and [GMP clearance for overseas manufacturers](#).

## 2.3 Indications and presentation

To be eligible for the assessed listed medicine pathway, the proposed product:

- must carry one or more intermediate level indication(s) (an indication that exceeds the list of permitted indications but is not a high level indication; see [Indications](#)). Products that carry intermediate level indications, including product-based restricted representations and certain indications referring to biomarkers, must go through the assessed listed medicines or registered complementary medicines pathway;
- must carry the intermediate indication(s) on the product label<sup>1</sup>;
- may carry optional additional low level indications which meet the criteria for a low level indication (for example, a permitted indication). Evidence to support these low level indications must also be supplied and pre-market assessed by the TGA;
- must not carry any reference to a prohibited representation;
- must carry all required label advisory statements, restrictions on dosage and restrictions on route of administration;
- must not have an unacceptable presentation, as specified in the subsection 3(5) of the Act and 3(A) of the [Regulations](#);
- must have a label assessed and approved by the TGA, and which meets the requirements of [Therapeutic Goods Order No. 69 - General requirements for labels for medicines](#) OR [Therapeutic Goods Order No. 92 - Standard for labels of non-prescription medicines \(TGO92\)](#); and
- must conform to every requirement relating to advertising specified in Part 5-1 of the Act and the [Therapeutics Goods Advertising Code](#).

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<sup>1</sup> The *Therapeutic Goods Act 1989* defines label as a display of printed information; on or attached to the goods, container or primary pack; or supplied with the container or pack.

The indications and presentation of the product will be pre-market assessed by the TGA. The only indications that can be used on the label are those that are assessed by the TGA and included in the ARTG entry.

Sponsors must ensure that the information contained in the application is correct. An incorrect certification could result in the product being cancelled from the ARTG under the provisions of paragraph 30(2)(bab) of the Act.

## 3. Indications

### 3.1 Risk categorisation

“Indications” are claims that relate to the purpose or health benefit of the product. They are defined in the Act as ‘the specific therapeutic uses of the goods’. All indications on the product label or other advertising must be included in its ARTG entry.

The TGA has a risk hierarchy of indications for complementary medicines. This takes into account the health status and potential vulnerability of the target population; the seriousness of any conditions mentioned; and the probability that a consumer may delay seeking medical treatment based on an indication. On the basis of these risk factors, indications are categorised into three levels of risk: low, intermediate and high.

- **Low level** indications are those appropriate for listed medicines, and are specified in the [list of Permitted Indications](#). They include indications for self-diagnosable, self-manageable, and self-limiting conditions where a delay in medical treatment would not be detrimental to the consumer. Low level indications may only refer to general health maintenance, health enhancement, prevention of dietary deficiency, or those that imply a benefit for a non-serious form of a disease or condition.
- **Intermediate level** indications exceed the criteria for low level indications but are still appropriate for listed medicines. They are generally more definitive, relate to more serious health conditions, and may present higher risk to consumers than low level indications. These indications include references to prevention or alleviation of non-serious forms of a disease, condition, ailment, defect or injury. Although the conditions captured by these therapeutic uses will generally be naturally self-limiting, self-diagnosable and/or self-manageable, medicines carrying these indications may have the potential to lead to a delay in seeking medical treatment and/or adverse consequences for the consumer.

Intermediate level indications can also include certain restricted representations<sup>2</sup>. These are indications which, despite referring to a serious disease, condition, ailment or defect specified in the Therapeutic Goods Advertising Code 2015 (as amended from time to time), are permitted on lower risk medicines in acknowledgement of a compelling health benefit from the use of products that refer to them. As such, in addition to demonstrating efficacy of the product, the public interest criteria need to be satisfied to allow a restricted representation to be used.

- **High level** indications are those that refer to the treatment, cure or prevention of a serious<sup>3</sup> form of a disease. The diseases referred to by this category of indication may not naturally resolve within a timely manner, and may have undesirable effects that may persist or worsen if effective treatment is not pursued in a timely manner. Products carrying high level indications are not suitable for listing, and must be registered in the ARTG following a complete assessment of their safety, quality and efficacy by the TGA.

The risk hierarchy for indications aligns with the classification of a medicine as a listed, assessed listed, or a registered product. This framework is summarised in Table 1 below.

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<sup>2</sup> A restricted representation is any reference expressly or by implication, to a serious disease, condition, ailment or defect. Prior approval is required by the TGA before an advertisement may refer to a restricted representation.

<sup>3</sup> A serious form of a disease or condition is one which is generally accepted to be beyond the ability of the average consumer to diagnose, evaluate, and/or safely treat without consulting a suitably qualified health care professional.

**Table 1: Indication risk classification**

Low level	Intermediate level	High level
<p>Indications drawn exclusively from the list of permitted indications.</p> <p>A low level indication <b>may</b> refer to:</p> <ul style="list-style-type: none"> <li>health enhancement</li> <li>health maintenance</li> <li>prevention of dietary deficiency</li> <li>a disease, ailment, defect or injury other than a serious form of those diseases.</li> </ul> <p>A low level indication <b>must not</b>:</p> <ul style="list-style-type: none"> <li>refer to, or imply, the prevention, alleviation, or cure of any form of a disease, ailment, defect or injury</li> <li>contain a prohibited representation</li> <li>contain a restricted representation<sup>4</sup></li> <li>have been specified in a non-permitted indications list (if such a list is made).</li> </ul>	<p>Indications that are not appropriate for the list of permitted indications, but are not high level indications.</p> <p>Intermediate level indications <b>may</b> refer to:</p> <ul style="list-style-type: none"> <li>the prevention, alleviation, or cure of a non-serious disease, ailment, defect or injury</li> <li>restricted representations (i.e. a serious form of a disease).</li> </ul> <p>Intermediate level indications may include those indications specified in a non-permitted indications list (if such a list is made).</p> <p>An intermediate level indication <b>must not</b>:</p> <ul style="list-style-type: none"> <li>refer to the prevention, alleviation or cure of a restricted representation (i.e. a serious form of disease)</li> <li>contain a prohibited representation.</li> </ul>	<p>Indications that refer to the prevention, alleviation or cure of a serious form of a disease, ailment or injury (i.e. restricted representations).</p> <p>A high level indication <b>must not</b>:</p> <ul style="list-style-type: none"> <li>contain a prohibited representation.</li> </ul>

See [Indications for assessed listed medicines](#) for examples of intermediate and low level indications.

## 3.2 How to structure an indication

Unlike sponsors of standard listed medicines who must draw exclusively from the list of Permitted Indications, sponsors of assessed listed medicines may submit their own indications. These indications should conform to the required structure and must be supported by appropriate evidence. A valid indication:

- must describe the specific therapeutic use(s) of the medicine; and
- must contain three core components: the context (if applicable), action and target.

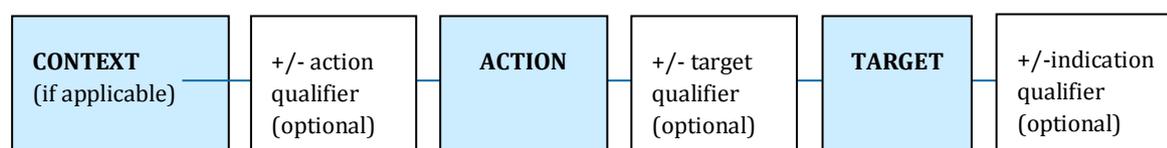
An indication may also be qualified to specify the severity, population, and timeframes related to the therapeutic use, depending on the specificity of the evidence. Components of an indication are summarised in Table 2.

<sup>4</sup> Excludes approved restricted representations for sunscreens, folic acid, vitamin D and calcium.

**Table 2: Components of an indication**

Component	Explanation	Examples
<b>Action</b>	The action, effect, mechanism or benefit of the product.	Reduces, relieves, supports, increases, maintains etc.
<b>Action qualifier</b>	Terms that ensure the action is suitable for the level of evidence the sponsor holds. They often specify effectiveness.	Helps, temporary relief of, etc.
<b>Target</b>	The physiological/ psychological factor or process; or disease, ailment, condition, defect or injury.	General health and well-being, headache, muscle cramps and spasms, fever, pain, etc.
<b>Target qualifier</b>	Terms that ensure that the target is suitable for the evidence the sponsor holds.	Mild, symptoms of, healthy/normal, moderate, excess, etc.
<b>Indication qualifier</b>	Terms that may provide information relating to the evidence held by the sponsor. This includes terms that specify a target population and/or times of use.	In the elderly, in sports athletes, in women, after strenuous exercise, etc.
<b>Context</b>	This specifies the traditional paradigm for indications where the sponsor holds evidence of traditional use.	Traditionally used in Western herbal medicines

The structure of a valid indication is illustrated below. The action and target are mandatory. The context is mandatory for traditional indications.



Note that the use of indication qualifiers requires sponsors to hold more specific evidence for their medicine.

## 3.3 Indications for assessed listed medicines

### 3.3.1 Intermediate (primary) indications

Intermediate level indications may only be used on products that have undergone pre-market assessment by the TGA. Assessed medicines must have at least one approved intermediate indication.

Please note that:

- Intermediate indications can be linked to individual ingredients or the entire medicine, provided that the evidence for the **finished product** supports the indications i.e. if the intermediate indication is associated with a specific ingredient (e.g. folic acid), evidence from clinical trials and/or biopharmaceutical studies on the product must be provided rather than literature based evidence for the specific ingredient (refer to [Evidence requirements](#)).
- As all indications for an assessed listed medicine must be supported by scientific evidence, indications that belong to a recognised paradigm outside modern conventional medicine (“traditional indications”) are not suitable as intermediate indications. They can, however, be included on products as secondary indications (see [Low level \(secondary\) indications](#)).
- Intermediate level indications can imply clinical efficacy where they are supported by evidence.

Intermediate indications may refer to:

- ***Preventing, curing or alleviating a non-serious form of a disease, ailment, defect or injury***

The indication may refer to or imply the prevention, alleviation or cure of a non-serious form of a disease, ailment, defect or injury. ‘Cure’ is considered to imply the complete resolution of the disease, ailment, defect or injury.

These indications may relate to:

- reduction in risk, frequency, duration or severity;
- relief or reduction of symptoms; and/or
- complete resolution;

of a non-serious form of a disease, condition, ailment, defect or injury.

Examples:

*‘Prevents muscular cramps and spasms’*

*‘Alleviates mild dermatitis’*

*‘Prevents cold sores’*

- ***A serious form of a disease, condition, ailment or defect***

The indication can refer to a serious form of a disease, condition, ailment or defect (e.g. a [restricted representation](#)) other than prevention, alleviation or cure of that disease, condition, ailment or defect.

These indications may relate to:

- relief or reduction of symptoms, without implying resolution, cure, alleviation (reduction in severity) or prevention of the disease, condition, ailment or defect.

Examples:

*'Reduces symptoms of tinnitus'*

*'Relieves rheumatoid arthritis symptoms, such as inflammation and pain'*

*'Relieves symptoms of gastroesophageal reflux disease'*



The list of permitted indications includes the indications covered by the substance-based restricted representation exemptions linked to vitamin D and calcium (referring to osteoporosis) and folic acid (referring to neural tube defects) on the basis of their public health importance, safe history of use and well-established evidence base. Current listed medicines can use these indications and are not required to transition to the assessed listed medicines pathway.

All other indications that refer to a restricted representation will require assessment and approval through a pre-market assessment pathway.

### 3.3.2 Low level (secondary) indications

Low level 'secondary' indications such as those drawn from the [list of permitted indications](#) may be included on assessed listed medicines in addition to the primary intermediate level indication(s). The secondary indications must meet the requirements for low level indications as described in the [Permitted indications for listed medicines guidance](#).

All secondary indications for use with assessed listed medicines require pre-market assessment by the TGA. Sponsors are required to submit evidence to support these indications alongside evidence submitted in support of the intermediate (primary) indications. The level of evidence required to support low level (secondary) indications for assessed listed medicines is consistent with the requirements for standard listed medicines.

Low level (secondary) indications can be linked to individual ingredients or the entire medicine, provided that the evidence for the **finished product** supports the indications.

Secondary indications may:

- be associated with individual ingredients or the whole medicine. If an indication is linked to a specific ingredient in the medicine's formulation, then that ingredient should be linked to that indication on the medicine's label;
- be general (non-specific) or specific in nature. General indications are those relating to health maintenance and supplementation or relief of symptoms not related to a named condition (e.g. 'helps soothe dry skin'). Specific indications refer to named conditions or symptoms, health enhancement or specific therapeutic effects (e.g. 'helps relieve indigestion');
- include both scientific and traditional indications, provided there is scientific evidence to demonstrate efficacy for all indications and evidence to show use in a traditional context for traditional indications.

## Scientific indications

Scientific indications are those that refer to modern conventional medicine paradigms and which are supported by quantitative scientific data derived from human clinical trials, observational studies and/or systematic reviews.

Scientific indications cannot:

- imply a higher level of certainty in the implied health benefit than warranted by the supporting evidence, i.e. terms such as 'clinically' and 'scientifically' in combination with 'proven', 'tested', 'trials' etc. are not appropriate unless supported by unequivocal data from robust clinical trials on the **product**;
- refer to traditional paradigms, or be based on evidence of traditional or historical use.

Examples:

*'Helps relieve mild dermatitis'*

*'Helps maintain blood levels of vitamin D'*

*'Aids/assists healthy red blood cell production'*



Vitamin or mineral supplementation indications are only permitted where the recommended daily dose of the product provides at least 25% of the Australian Recommended Dietary Intake (RDI) for that vitamin or mineral. If there is no Australian RDI for a vitamin or mineral, an RDI from another country may be used. Indications should not refer to the presence of vitamins or minerals unless they are present in the recommended daily dose of the product to at least the level of 10% of the RDI, unless there is evidence to support a therapeutic effect below this level. The dose must be consistent with the evidence to support the indication being made.

## Traditional indications

Traditional indications are those that belong to a recognised paradigm outside modern conventional medicine. These include - among many others - traditional Chinese medicine, Aboriginal and Torres Strait Islander healing practices, Ayurvedic medicine, and Western herbal medicine. Traditional indications must be based on long-term use (in excess of three generations - 75 years) within a specific paradigm. The traditional use should be extensively documented in internationally recognised evidence sources for traditional medicine use.

Please note, all indications for an assessed listed medicine must be supported by **scientific evidence** of efficacy. Claims of use in a traditional context may be used if the therapeutic use of the indication is supported by scientific evidence of efficacy. For example, 'traditionally used in Ayurvedic medicine to soothe an upset stomach' can be used if supported by; scientific evidence that the product relieves the relevant stomach condition; and evidence of a tradition of use in Ayurvedic medicine.

Traditional indications must refer to the traditional paradigm in which the medicine has been used, must use terms consistent with the specific traditional paradigm, and must be based on the experiences/use within the specific paradigm. They may include multiple traditions if the ingredient/product has been used within more than one tradition for the same benefit.

Example:

*'Ingredients in this medicine have been traditionally used in Ayurvedic and Chinese medicine for relieving symptoms of the common cold'*

Traditional indications must not:

- refer to scientific terminology, or use terms belonging to other traditional paradigms
- refer to anatomical, physiological or pharmacological effects not envisaged in the traditional paradigm (e.g. 'lowers cholesterol'), or requiring scientific substantiation; or
- refer to conditions that cannot be diagnosed within that paradigm.



It is important to ensure that your indication aligns with the evidence you have to support it. The supporting studies need to refer to medicines with the same formulation, preparation, dosage, and duration of use, and must have been carried out in a similar population group and context (refer to [Alignment](#) and [Presentation](#) for more information).

## 4. Application categories

Applications for assessed listed medicines are made under section 23B of the Act. There are three categories of application, L(A)1 – L(A)3. The increasing levels correspond to the increasing complexity of applications, and consequently, increasing data requirements, evaluation timeframes and fees.

It is important to ensure that you select the correct application category for your application in order to ensure that it can be accepted for evaluation.



This guidance provides descriptions of the three application categories. If your proposed application does not appear to be captured by a category, you can determine the appropriate application category by considering the data requirements for efficacy, which are outlined in Module 5 of the [Common Technical document \(CTD\) guidance](#).

### 4.1 Application category: L(A)1

This category includes products that are identical to an existing assessed listed medicine other than [permitted differences](#), such as its name, colour, printing ink, flavour and/or fragrance.

The following conditions must be met:

- The reference medicine<sup>5</sup> must have been fully evaluated for efficacy by the TGA.
- The reference medicine must comply with all current requirements and standards, relevant [Therapeutic Goods Orders](#) (e.g. TGO 77, TGO 78, TGO 80, TGO 92) and default [pharmacopoeial standards](#).
- Label, indications and formulation must reflect the fully evaluated reference medicine.
- Full access by the TGA to the reference medicine dossier must be provided. The sponsor of the reference medicine must authorise the TGA to access the information on the reference medicine files and ARTG record for the purpose of the application.

### Permitted differences

Table 3 summarises the list of differences that are appropriate for L(A)1 applications.

**Table 3: List of permitted differences for L(A)1 applications**

Difference	Description
<b>Sponsor details</b>	The sponsor of the flavour/fragrance/colour variant can differ from the sponsor of the reference medicine, provided the sponsor of the reference medicine authorises the TGA to access the information on the reference medicine files and ARTG record for the purposes of the application.

<sup>5</sup> Sometimes referred to as the 'innovator', 'originator' or 'parent' medicine.

Difference	Description
<b>Medicine name</b>	The proposed medicine name must be different to the reference medicine. The proposed medicine name cannot include a claim <del>or</del> indication that is not approved for inclusion in the ARTG entry or name of the reference medicine. Including a subset of the approved indications in the medicine name is not permitted.
<b>Manufacturing sites</b>	The manufacturing sites for the proposed medicine can differ from the reference medicine where the proposed manufacturer has been validated and shown to be equivalent or better. Ensure that you have valid evidence of GMP for the manufacturers.
<b>Flavour/fragrance/colour variants</b>	<p>Only the flavour, fragrance and/or colour agents can differ in the proposed medicine, and the combined total difference cannot be more than 2% w/w or w/v of the total formulation.</p> <p>The proposed raw material specifications for new flavour/fragrance/colour must comply with applicable standards, and all components are included in the <a href="#">Therapeutic Goods (Permissible Ingredients) Determination</a>.</p> <p>If the new flavour/fragrance/colour includes excipients that must be declared on the label, ensure that the labels have been updated accordingly. If the medicine label includes any claims that it does not contain a particular excipient (e.g. gluten free, sugar free, lactose free) ensure the claims are true in regard to the components of the new flavour/fragrance/colour.</p>
<b>Pack size</b>	The proposed pack size(s) can differ from the reference medicine only for solid dosage forms where there is no change in container material.
<b>Medicine labels</b>	<p>The labels for the proposed medicine must be identical to the reference medicine, other than the medicine name, design and layout, pack size details, sponsor or supplier details and logos.</p> <p>The proposed label graphics can differ from those approved for the reference medicine provided that:</p> <ul style="list-style-type: none"> <li>• they are consistent with the ARTG details for the medicine</li> <li>• any graphics that represent the action of the medicine directly correspond to an equivalent graphic approved for the reference medicine</li> <li>• the graphics comply with the guidelines (see <a href="#">Presentation</a>)</li> </ul>
<b>Finished product specifications / visual identification</b>	<p>The finished product specifications must be identical to those approved for the parent medicine other than the flavour/fragrance/colour (including printing inks) aspects.</p> <p>The visual identification can differ from the reference medicine only when it is either a direct consequence of the new flavour/fragrance/colour agent(s); or a difference in debossing/embossing/printing to remove or add identifying marks.</p>

## 4.2 Application category: L(A)2

This category is for generic medicines or medicines where a Comparable Overseas Regulator (COR) has demonstrated their efficacy.

### 4.2.1 Generic medicines

In comparison to the fully TGA evaluated assessed listed reference medicine, the proposed [generic medicine](#) must have the same:

- active ingredient(s) with same quantity;
- dosage form;
- directions for use;
- indications; and
- safety and efficacy properties.

The generic medicine must:

- be bioequivalent when compared to the reference medicine (meet the [Biopharmaceutic and pharmacokinetic requirements](#)); and
- provide a justification of the use of the particular combination of ingredients including potential interactions.

### 4.2.2 Medicine evaluated by a Comparable Overseas Regulator (COR)



The TGA is currently developing guidance for the use of evaluation reports from CORs. Guidance and a list of accepted CORs will be available on the TGA website in due course.

## 4.3 Application category: L(A)3

This category includes all products that are not covered by L(A)1 or L(A)2 and is either:

- a new medicine requiring a *de novo* evaluation of the efficacy of the product.
- a variation to an existing approved assessed listed medicine, where the medicine contains one of the following:
  - different active ingredient(s)
  - different strength (i.e. quantity of active ingredient(s))
  - different indication(s) (other than removing an indication)
  - different dosage form; or
  - different excipients.

L(A)3 applications must provide complete Module 1, Module 2 and Module 5, as applicable.

To demonstrate efficacy, L(A)3 applications must:

- provide efficacy evidence in line with Table 5 (using Method 1, 2A or 2B)
- meet the evidence requirements specified under [Evidence requirements and standards](#) and [Alignment of indications and evidence](#).

## 4.4 Variations to an existing assessed listed medicine

Once a medicine has been listed in the ARTG, the sponsor may request approval from the TGA to make changes to the application. Subsection 9D(1), 9D(2) and 9D(3) of the Act provides the circumstances under which a sponsor may request an amendment to the ARTG. These include:

- correction of an ARTG entry of a medicine that is incomplete or incorrect;
- certain safety-related variations to an ARTG entry of a medicine that reduce the patient population (such as by removing an indication), or have the effect of adding a warning or precaution (such as an adverse effect or interaction);
- other variations to an ARTG entry of a medicine, provided that the delegate of the Secretary is satisfied that the change does not reduce the quality, safety or efficacy of the medicine.



The TGA is currently developing the variation application types for assessed listed medicines.

### 4.4.1 Changes to labels

Once a product has been listed in the ARTG, the sponsor may request approval from the TGA to make changes to the label.

New draft labels must be supplied to the TGA with the application. Relevant changes must be highlighted (e.g. through the provision of 'track changes' labels or a table detailing all the proposed changes).

## 5. Evidence requirements and standards

This guidance provides information on the general types and standards of evidence required to support an application for an assessed listed medicine. Specific data requirements and dossier formats for individual application categories are provided in [Application dossier requirements](#).

### 5.1 Methods of establishing efficacy

#### 5.1.1 Overview of methods of establishing efficacy for different application categories

Each application category has different methods for establishing efficacy of the product. These methods are generally summarised in Table 4 below. The methods of establishing efficacy for **L(A)3 applications** are described in more detail in Table 5.

**Table 4: Overview of application categories and efficacy requirements**

Application type	Product type	Method of establishing efficacy
L(A)1	Identical to an existing assessed listed medicine, other than a permitted difference as specified in Table 3	<ul style="list-style-type: none"> <li>Assessment of label</li> <li>Access to reference medicine dossier required</li> </ul>
L(A)2	<b>Generic</b> medicine of a fully evaluated assessed listed medicine	<ul style="list-style-type: none"> <li>Meets the <a href="#">biopharmaceutic and pharmacokinetic study requirements</a></li> <li>Justification of the use of the particular combination of ingredients including potential interactions</li> </ul>
	<b>Identical</b> to a medicine evaluated by a <b>Comparable Overseas Regulator (COR)</b>	<ul style="list-style-type: none"> <li>Full un-redacted COR evaluation report</li> </ul>
<b>L(A)3</b> <ul style="list-style-type: none"> <li>Products not covered by L(A)1 or L(A)2</li> <li>Includes <b>new products</b> or <b>variation to an existing assessed listed medicine</b></li> </ul>	<b>Any type</b> of product	<ul style="list-style-type: none"> <li>Method 1</li> </ul>
	<b>Isolated chemical substances</b> (i.e. single chemicals, well-defined chemical complexes, prodrugs, amino acids, vitamins and minerals)	<ul style="list-style-type: none"> <li>Method 2A</li> </ul>
	Products that meet the requirements for a compliant <b>biowaiver</b> and medicines that <b>do not require biopharmaceutic studies</b> or clinical efficacy studies (e.g. some aqueous oral solutions or some products containing substances that are not systemically or locally absorbed)	<ul style="list-style-type: none"> <li>Method 2B</li> </ul>

## 5.1.2 Methods of establishing efficacy for L(A)3 applications

All indications for assessed listed medicines must be supported by scientific evidence of efficacy of the product. Efficacy refers to the potential of a medicine to produce a beneficial therapeutic effect in tightly controlled circumstances relative to a placebo<sup>6</sup> or other interventions. Efficacy studies focus on demonstrating statistically significant differences between intervention groups in clinical settings.

It is important to note that efficacy is not the same as effectiveness:

- **Effectiveness** refers to the extent of perceived or reported a beneficial effect under “real world” settings, and may be different than efficacy as a consequence of factors that are controlled or limited in clinical settings but not in real world use (e.g. different population groups, diets, etc.).
- **Efficacy** studies focus on establishing a causal relationship between a treatment and an effect. While medicines eligible for the assessed listed medicines pathway may operate through different therapeutic modalities to conventional medicines, there is no difference in the nature of either the cause-effect relationships being assessed or in the outcomes being studied. Similar principles and standards of efficacy evidence apply to these products. As a result, assessed listed medicines cannot solely be supported by evidence of effectiveness (e.g. historical use), and must be supported by evidence of the efficacy of the **finished product**, rather than simply the efficacy of separate ingredients.

For **L(A)3 applications**, there are three methods via which applicants may provide evidence of the efficacy of the proposed product (see Table 5). These three methods are designed to ensure that there is a sufficiently high standard of evidence to support consumer confidence in the indications, while being sufficiently minimalist to enable access to the pathway and support innovation in the sector. In brief:

- **Method 1** utilises the common standard approach of clinical trials on the product, and is suitable for **all product types**, including traditional medicines, herbal medicines, probiotics and conventional medicines.
- **Method 2A** uses a combination of efficacy data and bioavailability/bioequivalence data to support plausible efficacy of the product. It is appropriate for systemically acting **isolated chemical substances** (i.e. single chemicals, well-defined chemical complexes, prodrugs, amino acids, vitamins and minerals).
- **Method 2B** uses ingredient efficacy data in combination with product dissolution/ release data or *in vivo* pharmacokinetic studies to support plausible efficacy of the product. It can only be used for products that meet the requirements for a compliant **biowaiver**<sup>7</sup> and certain medicines that **do not require biopharmaceutical studies** or clinical efficacy studies (e.g. some aqueous oral solutions or some products containing substances that are not systemically or locally absorbed)<sup>8</sup>. See [Biopharmaceutical and pharmacokinetic studies](#) for further information.

Table 5 specifies the minimum requirements and may vary depending on the product<sup>9</sup>.

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<sup>6</sup> A placebo is a substance or treatment with no active therapeutic effect.

<sup>7</sup> A biowaiver is an acknowledgement that *in vivo* bioavailability and/or bioequivalence studies may be considered unnecessary for product approval.

<sup>8</sup> A study or justification may be required if there is doubt as to whether absorption occurs.

<sup>9</sup> For example, additional biopharmaceutical and pharmacokinetic studies may be required for non-conventional dosage forms such as [modified release products](#).

**Table 5: Methods for establishing the efficacy of assessed listed medicines**

Data type	Method 1	Method 2A	Method 2B
<b>Suitable product types</b>	All types	Systemically acting isolated chemical substances.	Supported by a biowaiver, or not requiring biopharmaceutic or clinical efficacy studies.
<b>Body of scientific information</b>	Full literature search report on the <b>finished product</b> <sup>10</sup> , or all active ingredients and formulation.	Full literature search report on <b>all active ingredients and formulation</b> .	Full literature search report on <b>all active ingredients and formulation</b> .
<b>Published studies or clinical study reports</b> (see Table 7)	Efficacy evidence on the <b>finished product</b> <sup>11</sup> .	Efficacy evidence for <b>each active ingredient</b> .	Efficacy evidence for <b>each active ingredient</b> .
<b>Biopharmaceutic and pharmacokinetic evidence</b>	Not normally required	Evidence for efficacy of the product formulation, established through: <ul style="list-style-type: none"> <li>a. bioequivalence data to existing products (consisting of evidence of release via dissolution data and absorption of the active ingredient via bioavailability data); or</li> <li>b. in some instances, comparative dissolution (against established data) demonstrating release of the active ingredient with appropriate scientific justification regarding bioequivalence.</li> </ul>	<i>In vitro</i> dissolution/ release tests or pharmacokinetic studies demonstrating <i>in vivo</i> drug release and availability of the active ingredients at the site of action.  Appropriate scientific justification of the approach and validation of the approach where appropriate.
<b>Formulation</b>	All methods must provide a justification of the use of the particular combination of ingredients, including potential interactions between the ingredients.		

Note that Methods 2A and 2B are generally not appropriate **for herbs, herbal extracts, substances of biological origin, or complex mixtures of chemicals**. This is due to the fact that the variable chemical composition and, in many cases, lack of known active component makes it difficult to accurately demonstrate appropriate biopharmaceutic properties of the medicine. A

<sup>10</sup> The finished product is the final dosage form with all active and excipient ingredients.

<sup>11</sup> Up to 2% of the total formulation can change compared to the formulation in the evidence, if the change is only to a flavour, fragrance and/or colour (including printing inks).

sub-set of chemical markers is not a suitable proxy for establishing the bioavailability or bioequivalence of all active constituents of a complex substance.

Applicants may submit a detailed scientific justification if the data package convincingly demonstrates that bioavailability/bioequivalence data is not required (see [Justifications](#)).



Products that do not meet the evidence requirements for Methods 2A and 2B may either be assessed via **Method 1**, or must be listed via the **listed medicines pathway** and use only permitted indications.

## 5.2 Types of applications

Some of the above evidence requirements for assessed listed medicines can be met through:

- **Conventional applications** - primarily contain full study reports of **company sponsored** studies that support the efficacy of the product. These studies can be supported with bibliographical references.
- **Literature-based submissions** - rely on **bibliographic data or overseas reports** to support the efficacy of the product (See [Literature-based submissions for complementary medicines](#)). The supporting literature must be relevant to the application. For example, the information should generally relate closely to the formulation, dosage regimen and indications of the proposed product. Unlike for prescription medicines, you do not need to gain approval of literature search strategies prior to submitting your application, and there is no formal pre-submission phase.
- **Mixed applications** - consist of a **combination** of full study reports of limited clinical studies carried out by the applicant supplemented with bibliographical references to support the efficacy of the product.

Regardless of the approach used, a certified translation should be provided for relevant evidence reported in a language other than English. All evidence will be subject to minimum requirements for relevance, quality and consistency.

If applicants utilise a literature based submission or mixed submission, all scientific publications should be peer-reviewed and be published in a reputable journal.

## 5.3 Literature search report

A literature search report is a description of a logical, transparent and reproducible approach to identifying and retrieving all authoritative published material which contains evidence (both positive and negative) related to the proposed product and/or its components. It is intended to provide a comprehensive and unbiased review of the available literature in relation to the application, and is a key requirement of all evidence-based medicine. It is not the same as a systematic review.

All applicants must include a report of the methodology used for the systematic literature search with the application in Module 1.5.1. The report should include, as a minimum, a well-conducted systematic search of [Medline](#) or [Embase](#) with descriptions of any additional non-systematic or manual searching. The report must outline:

- the search strategy, rationale, platform and date;
- references retrieved and period covered;

- selection or filter criteria applied to identify relevant reports;
- list of reports which have been excluded;
- appraisal of the evidence identified;
- pivotal studies and the rationale for their selection; and
- details of how any additional references were retrieved - for example, from in-house databases, lists of references, or hand searching.

For a search strategy to be considered robust it should be reproducible. Applicants should not substitute 'in-house' databases for Medline and/or Embase searches, or use internet search engines as a primary search platform. However, applicants may include other appropriate public databases in addition to Medline/Embase, and must include all relevant studies regardless of whether the findings are adverse to the proposed product or not. Relevant reports include all studies that reference (amongst others) the product ingredients, formulation, dose, health benefit, and context of use.

No single literature search strategy will fit all cases and requirements will vary according to the specific nature of the application.



In planning and conducting systematic literature searches, you may find it useful for an information retrieval expert to be involved in the process.

For more information on documenting literature searches, please refer to guidance on [Systematic literature searches](#) on the TGA website.

## 5.4 Standards of evidence

The evidence provided to support an application for an assessed listed medicine should cover aspects of the pharmacology, clinical safety (e.g. relating to the dose, use in vulnerable populations, specific formulation and dose form), and efficacy of a medicine, and serve to establish the balance of benefits and risks of the medicine in relation to its intended use. It should also provide the scientific evidence to support the claims and directions for use made on product labels and other product literature.

In assessing the evidence, the TGA must be assured that outcomes observed are due to the therapeutic action of the product and are not simply due to chance or sources of experimental bias introduced by the design, execution, or reporting of the study. The outcomes should also be clinically meaningful, and plausibly applicable to the wider population.

Overall, the standard and weight of evidence submitted for an assessed listed medicine should support a plausible cause-effect relationship between the treatment or intervention and the presumed therapeutic outcome. To ensure that such inferences can be made from studies, the standard of evidence submitted by applicants is reviewed on the basis of:

- the level of evidence (type/ design, and quantity of consistent evidence)
- evidence quality
- statistical validity
- external validity (generalisability)
- extent of evidence consistency
- relevance of the evidence to the product and indications

Information on these considerations is outlined below.

### 5.4.1 Level of evidence

The level of evidence refers to the type and quantity of studies used to demonstrate the claimed efficacy of a product.

Certain sources of evidence provide higher quality information in this regard than others due to their design, methodology or level of review, and consequently, the degree to which sources of bias have been limited. Additionally, certain types of studies are appropriate as support for both intermediate level indications and low level indications, whereas others are only appropriate for low level scientific or low level traditional use indications. The study type and the body of knowledge should therefore be carefully considered by sponsors in evaluating their evidence in supporting the efficacy of the product.

A brief overview of the main relevant study types and their utility is given below, but applicants may consult the National Health and Medical Research Council (NHMRC) publication: [How to use the evidence: assessment and application of scientific evidence](#) for a more detailed discussion.

#### Study types

##### *Clinical trials*

These are studies in which there is an intervention given by an investigator and the subject is followed prospectively through time. Clinical trials vary widely in the strength of evidence they provide, depending on the design and measures taken to reduce sources of error. Certain types of trials offer specific advantages and may mitigate some of the challenges of sampling and generalisation. Examples include:

- **Parallel group designs** - subjects are assigned to one or more treatment groups and followed through the study. The advantage of this approach is that it is very straightforward and very few assumptions are made.
- **Crossover designs** - each subject is assigned to a sequence of two or more treatments and acts as their own control for treatment comparisons. This reduces the number of subjects required to achieve an appropriate statistical power.
- **Multi-centre studies** - the intervention is delivered across multiple sites. This improves the chances of recruiting sufficient subjects for good statistical power, and may provide better generalisation of the results to the broader clinical setting. However, they are also subject to greater potential variability.
- **Factorial designs** - two or more treatments are studied simultaneously through the use of various combinations of treatments. The key advantage is that more than one intervention question can be examined within the one trial.

Well-conducted clinical trials can be used as evidence to support both intermediate level and low level indications. Clinical trials submitted as evidence to support an indication should be published in a high quality, peer-reviewed journal. Original unpublished clinical trials should meet all the applicable [TGA adopted guidelines](#).



Only human studies are considered appropriate to support indications for listed medicines. The scientific uncertainties involved in extrapolating non-human data from animal and *in vitro* studies limit their usefulness. However, non-human and *in vitro* studies may be used to support any discussion on biological plausibility, and *in vivo* and *in vitro* studies may be used when providing [biopharmaceutical and pharmacokinetic data](#).

## ***Systematic reviews***

Systematic reviews are characterised by an unambiguous research question; explicit and reproducible criteria for the identification and inclusion/exclusion of studies; a rigorous appraisal of the quality of individual studies; and a systematic synthesis of the results of included studies<sup>12</sup>. Statistical methods (meta-analysis) may or may not be used to analyse and summarise the results of the included studies.

A well-conducted systematic review provides a useful summary of clinical information, and may help resolve seemingly conflicting information. Systematic reviews can also potentially overcome issues related to small sample sizes, and be more generalisable to the wider population (see [External validity](#)). Reviews by the Cochrane Collaboration are generally well regarded.

While systematic reviews are a recommended source of evidence for assessed listed medicines, they can be subject to a number of weaknesses. The studies they cover need to be appropriately powered and conducted and reviewers have to consider inclusion criteria with prior knowledge of the results. This may lead to bias; and due to differences in study designs, endpoints, populations, the validity of combining data must be carefully considered. Applicants should critically appraise the methodology and conclusions of any systematic review to determine whether it supports the efficacy of their product.

In general, robust systematic reviews can be used as evidence to support both intermediate level and low-level indications.

## ***Observational studies (cohort and case-control)***

**Cohort studies** are prospective observational studies that involve comparison of two groups of subjects that are followed over time from exposure or non-exposure to a treatment to the subsequent outcome. The result is usually reported as a relative ratio of the outcomes in the two cohorts. Cohort studies are potentially cheaper and easier to conduct than randomised clinical trials, and are useful for assessing the relationship between intervention and the outcome of interest.

**Case-control** studies are retrospective observational studies. They commence from the outcome, and attempt to work backwards to the exposure. This requires identification of a group with a particular characteristic (cases), and a comparison group (control) that is as similar as possible to the case group but lack the trait in question. In these studies there is no direct intervention - information is obtained from direct questioning of the subject or consultation of records. Case-control studies are advantageous in offering a relatively inexpensive approach and short analysis timeframes. They also require a small number of subjects and do not suffer from the same subject attrition as cohort studies.

Case-control and cohort studies suffer from potentially significant sources of selection bias; potentially compromising attrition of subjects; and a lack of reliability for modest treatment effects. An additional major drawback in case-studies is the potential influence of confounding variables<sup>13</sup>, which must be mitigated via matching cases with controls with similar age, gender, socioeconomic status and so forth. As a result, cohort and case control studies are limited in their ability to provide unbiased and unambiguous data regarding the true efficacy of an intervention, and therefore may not provide acceptable evidence for some indications.

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<sup>12</sup> [Cochrane Collaboration - Glossary](#)

<sup>13</sup> A confounding variable is a factor that may contribute to an apparent association between an exposure and outcome by independently affecting both.

### ***Comparative studies (non-control)***

Single-arm (interrupted time series and case series) studies are prospective studies in which a group of individuals is exposed to an intervention and the response to the intervention measured at multiple time points or after the intervention. There is no control group. Single-arm studies are useful when the available subject pool is limited and it is therefore not optimal to randomise many participants to a control arm, or when it is unethical to employ a placebo control.

However, these studies are often limited by an inability to distinguish between the effect of the treatment, a placebo effect, and the effect of natural history. Additionally, they may fail to identify positive effects in situations where a negative outcome would have resulted in the absence of the intervention. They are, therefore, not appropriate as a sole source of evidence for the efficacy of an assessed listed medicine, but can be used as evidence in combination with other sources of evidence.

### ***Non-systematic reviews***

Non-systematic reviews tend to be mainly descriptive and often focus on a subset of studies selected by availability or author preference. They typically include an outline of the major findings of a collection of studies, and a broad appraisal of the overall body of literature. They do not employ an organised method of identifying, compiling, and evaluating studies using a set of specific criteria. Non-systematic reviews may or may not include a quantitative pooling of data (meta-analysis). Although informative, non-systematic reviews are limited by selection and author bias. They may also fail to provide clear conclusions, particularly if the studies included have conflicting results. Due to this, non-systematic reviews cannot be used as a sole source of evidence for efficacy, but can provide support for other studies.

### ***Comparable Overseas Regulator (COR) reports for L(A)2 applications***

Other international regulatory agencies evaluate and approve low risk medicines. Although they may have vastly different regulatory frameworks compared to Australia, the core scientific and technical methodologies employed by many of these agencies during scientific evaluation are largely similar. As a consequence, where the methodologies and standards employed by an agency are comparable to those used by the TGA, it is possible for applicants to submit technical data from CORs to support the efficacy of their proposed product.

However, a set of criteria relating to the international agency and the scientific report must be met. These criteria are **currently being finalised**. Once finalised, they will serve to ensure that best practice regulatory approaches have been employed. The requirements for the report will include the following:

- Reports must be complete, un-redacted, and written in English (or include a certified translation).
- The reports must collectively address all aspects of the evidence requirements for Module 5 (clinical).
- The report must have been fully written by an overseas regulator, and present an independent assessment of data provided to that regulator - i.e. self-affirmed/ self-assessed reports or 'expert opinion' reports are not acceptable.
- Reports should be prepared using internationally accepted guidelines and standards consistent with those used by the TGA.
- The characteristics of the medicine or ingredient and its intended use described in the report should be identical to that described in the sponsor's application. The formulation, dose, route of administration and/or indications described in the COR report(s) must be identical to that being applied for. Minor formulation changes for fragrance, flavour and

colouring variants are permitted, where the combined total difference is not more than 2% of the total formulation.

- There must be no new indications proposed beyond what the report(s) considered.
- There must be no new contradictory clinical data or regulatory evaluation reports available beyond what the evaluation report has considered.
- An application for the proposed medicine must not have been withdrawn in response to technical questions from a regulator or rejected in any other jurisdiction.
- The conditions under which the reports are provided should not preclude general information about the ingredient or medicine from being published (noting that commercial in confidence information would not be disclosed).

All COR reports should be included in Module 1 under 'Foreign evaluation reports' (1.11.4).

The TGA will not re-evaluate the efficacy data previously evaluated and approved by CORs. The TGA will review the COR assessment report and Australian label to ensure that the evidence meets all requirements and supports the indications and claims of the proposed product.

Reports may be used in conjunction, or in combination with independent scientific studies, provided that the medicines to which they refer are sufficiently similar, and the minimum data requirements are met. Reports from CORs that may not meet all criteria may be considered in certain instances, provided the applicant can provide adequate justification or additional data as required.

The use of international reports enables the TGA to conduct abridged evaluations that focus on issues that are specific to the Australian regulatory context, such as the product label. However, where overseas regulatory reports are used, the TGA will continue to make the final regulatory decisions, ensuring that safety, quality and efficacy are not compromised and that the Australian context is taken into account.

### ***Scientific reference texts and monographs***

Several internationally recognised monographs and reference texts are available and may be used to support secondary (low level) indications. Only sources that include scientific/ clinical information are appropriate to support secondary scientific indications. Some examples include:

- [European Food Safety Authority \(EFSA\)](#)
- [Joint FAO/WHO Expert Committee on Food Additives \(JECFA\) monographs](#)
- [European Scientific Cooperative on Phytotherapy \(ESCOP\)](#)
- [European Medicines Agency \(EMA\) monographs](#) (well-established use part only)

The monographs produced by a particular organisation may not all meet the specific requirements for assessed listed medicines. Applicants should ensure that the particular monograph provides appropriate scientific evidence to support their product's indications and claims.

### ***Traditional reference texts***

If your applications has indications that refer to use in a traditional context (these can only be low level indications), then it may use traditional evidence to support the context of traditional use (see [Traditional indications](#)).

Many traditional ingredients have a well-established period of widespread traditional use which is recorded in *materia medica*, monographs, pharmacopoeias and publications from various

international regulatory authorities. In some cases, traditional medicine practices have also been recorded in ethnobotanical or sociological papers. This provides an accumulated repository of information that reflects the refinement of dosage and formulation.

Traditional reference texts can be used to support traditional use indications provided that the dosage, formulation, preparation and use of the medicine are the same as that described in the evidence. Evidence of traditional use for an indication must demonstrate that the medicine or the relevant ingredients in the medicine has been used for at least three generations (at least 75 years) in the tradition it belongs to. In some instances, different sources of evidence of traditional use may be required to support a particular indication for an ingredient or formulation. Together these sources should form a combined collective of evidence that will be relevant and of high quality.

An official national pharmacopoeial monograph may be accepted as evidence of use during the years the monograph has been valid. However, applicants should note that most pharmacopoeias do not contain information on therapeutic indications, posology, or safety of a medicine, since their purpose is to detail the quality aspects.

For many traditional medicines there has been little quantifiable scientific research, scientific assessment or scrutiny undertaken on the medicine's mode of action or effect. It is therefore inappropriate to use evidence of traditional use to support a mechanism of action or an underlying physiological process, as these are required to be supported by scientific evidence (refer to [Indications](#)).

Some monographs refer to clinical studies or pharmacology of a particular ingredient using citations and reporting study outcomes of auxiliary scientific papers. Such information is considered a secondary source of scientific evidence and cannot be used to support traditional indications.

Some examples of sources of evidence for traditional use include:

- [European Medicines Agency \(EMA\) monographs](#) (traditional use part only)
- [WHO monographs on selected medicinal plants](#)
- British Herbal Pharmacopoeia
- Pharmacopoeia of the People's Republic of China Vol 1.



Non-reference textbooks, web searches, and publication abstracts are not appropriate sources of evidence to support an application for an assessed listed medicine.

## Evidence hierarchy and quantity

Double blinded randomised controlled trials and systematic reviews of multiple randomised clinical trials are considered to be the gold standard in epidemiological and clinical research, as they are most likely to achieve low bias and high precision when studying treatment effects. However, they are not always available or feasible. Acknowledging this, the TGA allows other study types and a range of other sources of evidence to be submitted as potential support for the claimed efficacy of a product. The limitations of these other sources need to be considered. For example, case-control studies and cohort studies may not be a practical means of providing evidence for some indications and are limited in their ability to produce unbiased and unambiguous data regarding the true efficacy of an intervention. They can, however, provide valuable supportive data relating to the likely effectiveness of an intervention for the general

population. Case studies and epidemiological surveys do not have sufficient strength in their own right to justify a scientific indication.

The TGA takes a 'weight of evidence' approach - the less robust the studies, the greater the quantity of consistent evidence required. To assist sponsors to ensure that they have at least the required minimum of appropriate level of evidence to support their application, the TGA has developed an evidence hierarchy and minimum evidence framework. These are provided in **Tables 6 and 7**. The definitions for intermediate and low level indications have been provided previously (see [Risk categorisation](#)).

Note that the requirements in Table 7 are generally **minimum** evidence requirements and the options presented may not be suitable for every situation. This represents the lower threshold below which the efficacy of the medicine cannot be reasonably assessed. Supplying the data in Table 7 is not sufficient for an application to be approved. The information must be of high quality and address the other requirements that address the efficacy of the product as set out in this document (see [Evidence requirements and standards](#) and [Alignment of indications and evidence](#)). Information on specific areas of concern may need to be addressed through more or better quality studies.

Additional studies serve to strengthen the evidence of efficacy, particularly if any of the pivotal studies are limited in some way, and may improve the likelihood of an application being approved.

Regardless of what studies are used, all sources of evidence must meet the evidence standards and include a full description of the study design, population, treatment(s) and protocols employed. Abstracts, web searches or incomplete references will not be accepted as suitable evidence. An overview of some of these considerations is provided in the following sections.

**Table 6: Evidence hierarchy for assessed listed medicines**

Category A	Category B	Category C	Category D
Double blind randomised controlled trials (including cross-over trials)	Observational studies e.g. cohort and case control studies	Non-systematic, generalised reviews - including databases	Traditional reference text
Systematic reviews	Comparative studies (non-control)	Publicised international regulatory authority articles	Herbal monograph
		Evidence based reference text - scientific	Herbal pharmacopoeia
		Scientific monographs	<i>Materia medica</i>
			Publicised international regulatory authority articles - Traditional only

**Table 7: Minimum evidence requirements for assessed listed medicines**

Indication <sup>14</sup>	Primary (intermediate)	Secondary (low level)	
Indication type	Scientific	Scientific	Traditional <sup>15</sup>
Required evidence	Minimum of one from Category A  OR  Minimum of two from Category B, AND one from Category C	<b>Non-specific indications:</b>  Minimum of two from Category B or Category C	<b>Non-specific indications:</b>  Minimum of two from Category D to support the tradition of use
		<b>Specific indications:</b>  Minimum of one from Category A  OR  Minimum of one from Category B, AND two from Category C	<b>Specific indications:</b>  Minimum of two from Category D to support the tradition of use  Plus  Additional evidence from Category C or Category D to support the specificity of the traditional indication

To meet the above minimum evidence requirements, the evidence should contain **independent sources of information** e.g. two publications referencing the same clinical trial or information are not considered to be two independent sources of information.

## 5.4.2 Study scope

### Conduct

All studies should be conducted according to [Good Clinical Practice \(GCP\)](#) principles and have appropriate ethical certification. They should also be compliant with [International Council for Harmonisation \(ICH\), and European Medicines Agency \(EMA\) guidelines adopted by the TGA](#) at the time of application. These can be accessed on the TGA website.

In particular, it is important for applicants to ensure that any studies:

- are conducted in accordance with sound ethical principles and have received prior approval by an independent ethics review committee.
- involve only participants who have freely given informed consent prior to the start of the study.
- are conducted by individuals that are appropriately qualified by education, training, and experience to perform their respective tasks.

<sup>14</sup> See definition in [Risk categorisation](#)

<sup>15</sup> All indications for assessed listed medicines must be supported by scientific evidence of efficacy, however traditional evidence is required to support use in a traditional context (see [Low level \(secondary\) indications – Traditional indications](#))

- include accurate recording, handling, and storage of information in a way that allows its accurate reporting, interpretation and verification.
- are scientifically sound, and described in a clear, detailed protocol.
- report any conflicts of interest.

The [Consolidated Standards of Reporting Trials \(CONSORT\)](#) guidelines provide a useful checklist against which the trial procedures can be measured, and helps standardise the ways in which the findings are reported. A related document, the Quality of Reporting of Meta-analyses (QUOROM) statement, provides specific guidelines for the reporting of meta-analyses, as well as a checklist to promote standardisation and the inclusion of critical components. Applicants may find these useful ways to self-assess the quality of the studies prior to submitting an application.

## Population selection

The study population used should be **appropriate for the outcomes being tested** (e.g. healthy individuals, women, elderly adults etc.). Data obtained from studies using participants with serious health concerns is generally not appropriate to support an indication for assessed listed medicines; **unless** the indication relates directly to a population with that condition (e.g. a restricted representation). In some circumstances it is also possible to use studies of participants with serious health concerns where positive outcomes were noted, to provide secondary (non-pivotal) sources of evidence.

The study population should be clearly identified in the study protocol, and all the inclusion and exclusion criteria adequately outlined. These criteria are particularly important. If the criteria are too lax, the validity of the inclusion may be questionable, while if the criteria are too tight, the results may not be applicable to the wider population (refer to [External validity](#)).

Baseline characteristics of treatment and control groups should be documented to ensure equivalence in key areas such as age, weight, diet and other factors that may contribute to non-treatment differences in health benefit between groups.

## Sample size

Studies submitted in support of the efficacy of an assessed listed medicine should involve a sufficient number of participants to enable the reliable detection of clinically significant treatment effects.

The number of participants required to be reasonably certain of a reliable result is described as the 'power' of a study. In formal terms, the power of a study is the likelihood of the study finding a true difference between treatments if one exists. The larger the sample size, the greater the statistical power of the study.

The number of study participants required for a study to demonstrate clinical significance depends on the study aim and design, how the data will be analysed, and the attrition/ drop-out rates. It may also be affected by:

- The size of the difference to be detected. The required sample size to achieve a particular power is inversely proportional to the square of the difference to be detected.
- The relative size of the samples. Greatest power is achieved with an equal allocation of subjects to treatment and control groups.
- The proportion of subjects who experience the treatment outcome.
- The extent of variation in the outcome. The larger the variation in the outcome, the greater the required sample size.

- The extent of protocol compliance. The worse the compliance, the greater the sample size needed to retain adequate power.

Many studies are undertaken with an unrealistic expectation of the likely size of the treatment effect, and the impact of variation and non-compliance. This may dramatically affect the acceptability of the conclusions. Applicants should therefore carefully consider any limitations of the statistical calculations that the study authors have reported, including the number of drop outs and the impact this may have on the reported study outcomes.

To ensure that a study is capable of supporting the indications for a product, the power should be at least 80%. The study should also provide a description of how the power/ sample size was determined. Underpowered studies may be submitted as supplementary evidence, however cannot be used as primary evidence due to the statistical uncertainty of the effect.



Studies submitted to support indications must have a statistical power of at least 80%.

### Study outcome(s)

The primary variable of a study is the measurement that provides an estimate of the effect or outcome of a treatment. Ideally, studies should only have one primary variable that:

- is the most clinically relevant to the proposed indication, and consequently, the one capable of demonstrating the efficacy of the medicine to the greatest extent.
- provides a reliable and validated measure consistent with the standards and norms of the relevant field.
- is clearly defined in the protocol before the start of the study. This is to avoid artificial result selection via post-hoc definition of the outcome.

If possible, multiple measures should be used.

Secondary endpoints assess other effects of the medicine that may or may not be related to the primary endpoint (e.g. questionnaires to assess subjective pain). If a study includes secondary efficacy outcomes, they should provide supportive evidence for the primary outcome, or provide supportive evidence for secondary outcomes specified and defined in the initial protocol. It is important that these methods are accurately validated, to ensure the results can be reproduced.

In some instances, the direct measurement of a clinically relevant benefit will be neither feasible nor practical (e.g. for the demonstration of a long-term health benefit). In such circumstances a surrogate variable, which relates to a clinically important outcome but does not in itself measure a clinical benefit, may be used. The surrogate variable must be a demonstrably valid and reliable predictor of clinical benefit.

In all cases, applicants should provide a justification addressing the clinical relevance of the outcome and the rationale for its selection. Additionally, they should demonstrate that the methods used to measure the variables that contribute to the study endpoints should be validated and meet appropriate standards for accuracy, precision, reliability, reproducibility, and responsiveness. Results for every measured outcome must be reported, regardless of whether they are positive, negative or non-significant. The report should also report and discuss any side effects or adverse events observed.

### 5.4.3 Study quality (internal validity)

In assessing the suitability of the evidence to support indications for assessed listed medicines, TGA evaluators review the quality of the studies submitted. In this context, quality refers to the extent to which the design of the study eliminates sources of bias, and therefore, provides confidence in interpreting the results.

Some of the important considerations for assessing the internal validity of evidence submitted are outlined in the sections below. They are, however, dealt with in greater detail in [TGA adopted guidelines](#). The NHMRC publication: [How to use the evidence: assessment and application of scientific evidence](#) also provides further useful information on many of these points.

While these principles are mostly applicable to studies used to support intermediate level indications (i.e. studies in Category A and B in Table 6), it is worthwhile applying them to studies submitted in support of low level indications, as this will improve the likelihood of an application being approved.

#### Sources of bias

The ideal experimental design should compare two groups that do not differ in any significant respect apart from the treatment or intervention of interest. Significant differences between the groups may introduce bias into the comparison. Bias is the tendency of any factors associated with the design, conduct, analysis and interpretation of the results of a study to cause the treatment effect deviate from its true value. Bias can be introduced through deviations in conduct (operational bias), or may be inherent in the design and analysis of the study (statistical bias).

The following examples of factors introducing bias can be considered when assessing the strength of a study:

- selection bias - study subjects are chosen in a way that results in a non-random sample that is not representative of the population.
- measurement bias - investigators may subconsciously favour, or more diligently pursue observations, in one treatment arm over the other and this can be reflected in the measurements obtained.
- observer bias - the observer makes a subjective appraisal of the outcome.
- recall bias - patients know whether they were allocated to the treatment group or the control group, and this affects their reporting of their symptoms.
- regression to the mean - a phenomenon occurring when groups have been selected on the basis of extreme scores. If the first measurement is an extreme score, the second measurement will tend to be closer to the average.
- treatment selection bias - the effects of a treatment are determined by confounders (e.g. other co-interventions) rather than the treatment itself.

#### Control, randomisation and blinding

Many sources of bias can be addressed through the use of appropriate controls, randomisation, outcome selection, and blinding of both researchers and patients.

- A control is an observation or treatment designed to provide a comparator in order to enable researchers to identify the effects of variables other than the treatment or intervention under study. Controls may be negative/placebo (to ensure that there is no effect of a placebo when no effect is expected), positive/known active (to ensure that an

effect can be measured when an effect is expected), a different dosage regimen, or no treatment. The choice of the control group is determined by such factors as the availability of standard treatments, the severity of the condition, and ethical considerations. The choice of control should be justified in the applicant's report.

- Randomisation is a method in which subjects are allocated by a chance mechanism to treatment or control groups. Each subject in the study should have the same chance of being allocated to any of the treatment groups. This eliminates selection bias; helps ensure that treatment groups will tend to be comparable; and ensures the validity of the statistical analysis. Ideally the randomisation process should be centralised and computer-based, and also incorporate concealment of allocation.
- Blinding is a statistical bias reduction technique in which the study participants have no knowledge of which treatment (placebo or test product) they received. Double blinding is where neither the study participants nor the investigators carrying out the study are aware of the treatment to which the subjects have been allocated. Double-blinding eliminates the potential for observation bias, and reduces the potential for the "placebo-effect". Blinding of outcome measurements becomes more crucial as the measure becomes more subjective and more open to observer bias. This is particularly important for symptoms and other patient self-report measures.

Applicants should take into account the controls, randomisation, blinding, and allocation concealment (where appropriate) when assessing the reliability of their evidence as support for indications. Well-designed and conducted studies should include a detailed description of the subject eligibility criteria, method of randomisation, and blinding technique employed so as to enable assessment of the potential for error or unblinding. Studies that do not employ or report these bias reduction techniques are less likely to be accepted by evaluators as convincing evidence of the veracity of claims.

## Changes to the protocol

Departures from the planned conduct of a study may introduce operational bias. It is therefore important that any evaluation of a clinical study report consider the number and severity of protocol violations and deviations and the completeness of patient follow-up. These may include changes to the inclusion or exclusion criteria, outcomes measured, group sizes, treatment protocol, blinding, and/or duration. Any statistical consequences of these changes and revision of analytical approaches should also be addressed.

## Dealing with missing data

One of the problems with clinical studies, particularly longer-term studies, is that data may be lost due to patient dropout, treatment failures, non-compliance, adverse events, and missed measurements, among other factors.

Missing data stemming from high attrition rates can lead to non-comparability of treatment and control groups, a reduction in the statistical power of the study, and the introduction of significant bias. This may make the results of the study difficult to interpret, and diminish the ability of the study to support an indication or claim.

Consequently, the design and conduct of a clinical trial should seek to minimise the amount and/or impact of missing data and where relevant, should contain:

- the subject withdrawal criteria
- whether and how subjects were replaced
- procedures for monitoring subject compliance

- procedures for accounting for missing, unused and spurious data
- subject accountability, including details for reasons of withdrawal
- a discussion of the number, time, pattern and possible implications of missing values.

The TGA will consider the reasons for the missing data, whether appropriate replacement methods were used, and the likely effect of any missing data on the study results.

There is no clear definition of what proportion of missing data would mean that a trial was not suitable to support any specific indication or claim, but in broad terms, 5%-10% would generally not be of great concern, while >20% would mean that missing values would need to be one of the key issues addressed in the evaluation.

#### **5.4.4 Statistical validity**

Statistical validity refers to the extent to which a measurement is well-founded and accurately reflects reality. The validity of the conclusions of the study is critically dependent on the nature of the metric used to measure an effect, the size of effect, and the type of statistical transformations and analyses performed.

Studies submitted as part of an application for listing of an assessed listed medicine must use valid statistical methods to assess the outcomes, and must account for any potential confounders. These statistical methods should be fully described in the protocol, and should be appropriate for the efficacy outcomes measured. Unplanned analyses undertaken after the completion of a trial (post-hoc analyses) are to be avoided as they are unlikely to have been considered in power calculations and study design.

#### **Analysis set**

In general, the main analysis should be in the intention-to-treat (ITT) population. This involves analysis of subjects according to the allocated treatment regimen, rather than the actual treatment experienced (i.e. subjects are analysed according to their allocation, regardless of their compliance to the treatment). This is the most conservative approach as it biases the analysis towards the null hypothesis. However, it serves to minimise bias in instances where the dropout rates are high.

When an ITT is performed, all efforts should be made to obtain outcome measurements from all original participants at the end of the study. In cases where this is not possible, baseline measurements of study parameters should be carried forward (for example, for a study outcome related to weight loss, body weight recorded at the beginning of treatment would be the same at the end of the study). A treatment effect demonstrated in an ITT analysis may underestimate the efficacy of the treatment, but may be a good reflection of effectiveness under real world conditions.

Applicants should be cautious of studies employing a per-protocol analysis. This is an analysis on the subset of study subjects that actually complied with the protocol sufficiently. While it is less conservative than ITT analysis, it maximises the chances of an effect being observed and is heavily prone to bias as adherence to the protocol may be related to the treatment outcome.

#### **Measure of the effect**

There are a large number of ways of expressing the effect of a treatment. These include averaged differences, standardised differences, weighted means, relative risk/ risk ratio, and odds ratio, among others. The choice of measure largely depends on the study design, and whether the outcome measured is a continuous number (e.g. blood pressure) or discrete (e.g. improved/ not improved).

For assessing efficacy, the risk difference and the number-needed-to-treat are the most important measures:

- The risk difference (also known as the absolute risk reduction or absolute effect) is the difference between the proportion or rate of events in the treatment group and the control group i.e. Risk Difference = Proportion treatment – Proportion control. It is the inverse of the number-needed-to-treat.
- The number-needed-to-treat is the number of patients that need to be treated with the test product before one patient experiences a clinical benefit from treatment. It is the inverse of the risk difference i.e. Number-needed-to-treat = 1/risk difference.

Only expressing the effect of a treatment as relative measures (e.g. relative risk/risk ratio, odds ratio) has the potential to mislead, as relative measures tend to exaggerate estimates of efficacy.

## Statistical significance

Even if the study is well-conducted and sources of bias are limited, there is a possibility that the results arose purely by chance. It is therefore essential that studies submitted as evidence for assessed listed medicines use appropriate statistical methods to minimise Type I errors. A Type I error (false positive) is a conclusion that there is a difference between two treatments when no difference exists in reality.

Well-conducted studies will usually report the degree of statistical significance (p-value) associated with the observed difference between treatments. The p-value provides an indication of the probability of claiming that there is a treatment effect when in fact there is no real effect (i.e. the probability of making a Type I error). The p-value provides an indication of whether the treatment effect that has been observed can be explained by chance alone. Although there is no definitive p-value threshold, the lower the p-value the greater the likelihood that the effect observed is real. In practice, a 'p' value of less than 0.05 indicates with acceptable certainty that an observed effect or health benefit is unlikely to be due to chance.

In considering the strength of their evidence, applicants should ensure that:

- the statistical test used to derive the p-value is appropriate and reliable;
- the p-value obtained for the primary outcome is less than 0.05; and
- all the actual p-values (not just  $p < 0.05$ ) are reported.

It is important to bear in mind that statistical significance does not provide information about the degree of benefit produced or whether it is likely to be clinically meaningful.

## Confidence

The confidence interval (CI) is the range of values within which there is a certain likelihood that the true value can be found. The confidence level is the probability that the CI contains the true difference. Well-conducted studies should usually report the 95% CI. This means that there is a 95% chance that repeated experiments would have outcomes that fall within the specified range.

The precision (or width) of the CI is also an important consideration. A narrow 95% CI is much more desirable than a wide 95% CI. A wide CI indicates a low level of confidence in what the true population effect is. The effect of different is illustrated in part in Figure 1.

When 95% confidence intervals are generated for primary study outcome measures, the 95% CI should include only clinically important treatment effects. The 95% CIs of the intervention and exposed groups must not overlap (refer to Figure 1).

## Clinical significance

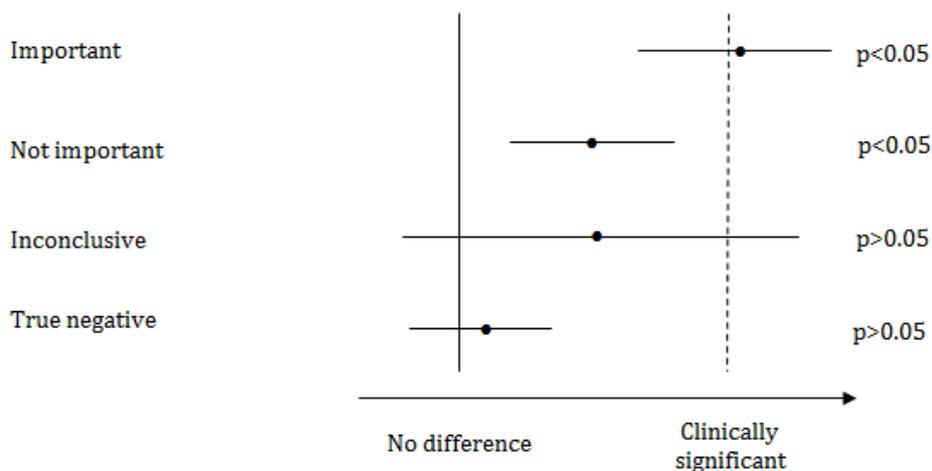
A statistically significant outcome indicates only that there is likely to be a relationship between intervention and outcome. For a study to provide adequate support for an indication, the observed differences should not only be statistically significant, but also be clinically meaningful.

Clinical significance is the degree of benefit that is worthwhile to justify a particular treatment or intervention. It can be regarded as a measure of how meaningful a particular study outcome might be to the consumer. For example, a study might demonstrate a statistically significant weight loss, but in practice, that effect would not generally be experienced or noticed by members of the wider population, and would be unlikely to significantly advance health goals.

Judgements about clinical significance are often made by experienced clinicians within a context of ongoing monitoring and supervised care. As assessed listed medicines are self-selected and often used without healthcare practitioner intervention or supervision, it is challenging to evaluate how studies result to practical health outcomes. This is particularly true given that the meaningfulness of a predetermined “significant clinical benefit” may vary between patients depending on a number of factors such as state of disease, comorbidities, personal circumstances, and alternative options for treatment.

Nevertheless, applicants should give consideration to the likely meaningfulness of an observed health outcome to the intended target population. In making such judgements, it is useful to consider the significance, confidence interval, confidence level, and the magnitude of the treatment effect. For the evidence to suggest that an intervention is useful, the 95% CI at  $p < 0.05$  should include only clinically important treatment effects. This is illustrated in Figure 1.

**Figure 1: Illustration of the impact of the size of the effect and the precision of the 95% CI on the interpretation of the outcomes of a clinical study.**



For a study to be considered as reliable support for an indication, the p-value for an observed difference should be  $< 0.05$ , and the 95% confidence interval should include only clinically meaningful results.

### 5.4.5 External validity

External validity and extrapolation are extremely important considerations in determining the scope of an indication.

Extrapolation is the application of results from a study to a different population from the one used in the study (e.g. results from a study on 20-25 year old women being applied to 30-35 year old women). Generalisability (or external validity) is a term often used to conceptualise the extent to which study results can be broadly generalised beyond the setting of the study and the particular sample groups used.

The validity of such inferences depends on the representativeness, size and variability of the study sample. The greater the extent of these characteristics, the more generalisable the results. Additional factors to consider when determining if the results of a particular study can be extrapolated or generalised are:

- The effect of gender, age, or ethnicity. Are physiological differences likely to impact on the efficacy of the treatment?
- The timing of the treatment. The stage of the condition /illness may impact on treatment outcomes.
- Variations in the condition being treated. There may be distinct underlying aetiologies despite similar presentations.

It is also worthwhile considering whether the results of a particular study are applicable to individuals as well as groups.

### 5.4.6 Balance of evidence and conflicting results

The strength of evidence provided by a specific study is greatly enhanced if the effect is reproducible, and if the cause-effect relationship proposed is consistent with existing knowledge.

A well-conducted [literature search](#) will identify all related studies, and these should be assessed in relation to the findings of the primary evidence. Positive, null and negative results should be examined. If there are **conflicts in the outcomes** of different studies, the applicant must provide a plausible explanation for the conflicts in a scientific **justification**.

In some instances, the conflicts can be readily accounted for by differences in design or methodology (e.g. dose form, population, timing etc.). If suitable explanations for the discrepancies cannot be found, the highest quality studies will receive higher weight in the evaluation.

### 5.4.7 Summary of considerations for studies

Table 8 summarises many of the considerations outlined in the preceding sections. Applicants may find it helpful in appraising the quality of their evidence prior to submission of an application.

It is important to bear in mind that these principles reflect issues that are taken into account in an ideal study. If there are valid scientific reasons for a particular omission or deviation, applicants can submit a scientific justification which addresses the matter (refer to [justifications](#)).

Applicants may find the following guidance useful:

- [Note for Guidance on Good Clinical Practice - Annotated with TGA comments](#)

- [Note for Guidance on General Considerations for Clinical Trials](#)
- [Note for Guidance on Statistical Principles for Clinical Trials](#)
- [Note for Guidance on Choice of Control Groups in Clinical Trials](#)
- [Guideline on Missing Data in Confirmatory Clinical Trials](#)

**Table 8: Principles for clinical trials, including trials included in systematic reviews.**

Topic	Consideration	Principle
Scope	Conduct	<ul style="list-style-type: none"> <li>• The study should be conducted using Good Clinical Practice (GCP).</li> <li>• The intervention must be described at a level that allows replication.</li> <li>• Conflicts of interest should be reported.</li> </ul>
	Sample	<ul style="list-style-type: none"> <li>• The report must specify the sample and how it was obtained, including inclusion/ exclusion criteria.</li> <li>• The study population must be appropriate for the outcomes tested.</li> <li>• The sample size should provide sufficient statistical power.</li> </ul>
	Outcomes	<ul style="list-style-type: none"> <li>• The stated outcome(s) of the intervention must be measured.</li> <li>• The outcomes should be appropriate and relevant.</li> <li>• Valid measures of the targeted effect must be used.</li> <li>• Results for every measured outcome must be reported, regardless of whether they are positive, negative or non-significant.</li> <li>• Potential side-effects or adverse events should be measured.</li> </ul>
Quality	Controlling bias	<ul style="list-style-type: none"> <li>• The methodology should include appropriate blinding or masking.</li> <li>• The design must have at least one control condition that does not receive the tested intervention (where relevant).</li> <li>• Where possible, assignment to conditions needs to minimise statistical bias through randomisation.</li> <li>• Measures of internal consistency must be included.</li> </ul>
	Changes and missing data	<ul style="list-style-type: none"> <li>• Protocol violations and deviations and the completeness of patient follow-up should be reported.</li> <li>• Compliance / attrition should be reported and accounted for.</li> <li>• Missing data must be reported and handled appropriately.</li> </ul>
Statistics	Basis	<ul style="list-style-type: none"> <li>• The intention-to-treat (ITT) population should be used.</li> <li>• The absolute risk difference and the number-needed-to treat should be reported where possible.</li> </ul>

Topic	Consideration	Principle
	Analysis	<ul style="list-style-type: none"> <li>Statistical methods must be relevant to the experimental design, and aim to produce an unbiased estimate of relative effects along with a statistical measure of confidence.</li> <li>Pre-test differences should be accounted for.</li> <li>The p-value or interval must reasonably exclude chance.</li> </ul>
	Significance	<ul style="list-style-type: none"> <li>Outcomes should have clinical, rather than merely statistical, significance.</li> <li>Efficacy can only be claimed for a consistent pattern of statistically significant effects.</li> <li>The extrapolation and generalisability of the results should be considered.</li> </ul>
Balance of evidence		<ul style="list-style-type: none"> <li>Evidence from multiple sources is desirable.</li> <li>Plausible explanations for contradictory results should be provided.</li> <li>Where two or more studies are available, the results of the highest quality studies will have higher weight.</li> </ul>

## 5.5 Biopharmaceutic and pharmacokinetic studies

Biopharmaceutic and pharmacokinetic studies are a critical part of establishing the efficacy of medicines. These types of studies demonstrate that medicines dissolve and release active ingredients appropriately; and that the active ingredients are absorbed, distributed and metabolised in a manner that allows efficacious quantities to reach the intended site of action. They also serve to ensure that undesirable effects such as dose-dumping, dose retention or *in vivo* interactions do not either reduce the efficacy of the product or pose a risk to the consumer.

For [L\(A\)3 applications](#) (using [Method 2A or 2B](#)) and [L\(A\)2 generic applications](#), different biopharmaceutic and pharmacokinetic studies are required to ensure that the products are likely to be efficacious. The data requirements are summarised below depending on the type of product. For further guidance see [TGA Guidance 15: Biopharmaceutic studies](#)<sup>16</sup>.



Pharmacokinetic data is not explicitly required when a clinical study is used as the main evidence for an intermediate indication (Method 1), however it is expected that such studies will address relevant aspects of the medicine's pharmacokinetic properties.

### 5.5.1 New products (systemically acting)

For [L\(A\)3 applications](#), in order to establish the efficacy of a new systemically acting product, applicants must provide bioavailability studies. This is particularly important in the case where the evidence is derived from efficacy studies on the individual ingredients (Method 2A), however as described in Table 5, is not usually necessary for Method 1.

<sup>16</sup> Although this guidance refers to prescription medicines, the same principles apply for providing biopharmaceutic studies for the relevant assessed listed medicines application types

Bioavailability is the proportion of the administered dose of an active ingredient that reaches systemic circulation as an intact drug. It may differ between individuals and depends on a large number of factors that cannot usually be reliably inferred from the formulation. For systemically acting oral products these include the:

- rate and extent of the disintegration of the product, and the rate and extent of dissolution of the active ingredient(s).
- rate and extent of passage of the active through the gut membranes - a process determined by factors such as the physiochemical characteristics of the active, including its lipid solubility, diffusivity and propensity towards interactions with active transporters in the gut wall, as well as the excipients used in the formulation, the drug coatings, and the gut lumen pH;
- rate of gastric emptying/ intestinal transit; and
- extent of first-pass metabolism in the liver - if first-pass metabolism occurs, some proportion of the substance will be removed before the remainder reaches systemic circulation.

For these reasons, applications for new assessed listed products must address several issues that impact on the efficacy of the medicine. These requirements also differ depending on whether the product is intended to be an immediate release product or a delayed/ modified release product.

### **Immediate release oral dosage forms**

The following studies (or a robust scientific justification for not including such studies) are required:

- a. study to establish that the proposed formulation is optimal (e.g. a comparative bioavailability study versus an oral solution of the drug);
- b. bioequivalence studies between the proposed formulation and pivotal clinical trial formulations;
- c. bioequivalence studies amongst the various strengths proposed in the application (if applicable); and
- d. a food effect study.

### **Modified release oral dosage forms**

Modified release products (including delayed, sustained, and combination release products) must be determined to meet the modified release claims; should provide consistent pharmacokinetic performance between dosage units; and should produce plasma concentrations that lie within the therapeutic range.

The following studies (or a robust scientific justification for not including such studies) must be submitted, *in addition to* the studies required for immediate release oral dosage forms:

- a. steady state versus an appropriate immediate release reference product; and
- b. *in vitro* and *in vivo* correlation studies.
- c. *in vitro* studies confirming the absence of dose-dumping effects in the presence of alcohol.

## 5.5.2 Generic products

For **L(A)2 and in some cases for L(A)3 applications**, the proposed assessed listed medicine may be similar or identical to an existing product for which bioavailability data exists. This includes products currently approved as an assessed listed medicine in Australia, evaluated by comparable regulatory authorities, or extensively studied in clinical trials, and excludes 'grandfathered' products. In such cases, the efficacy of the proposed product can be inferred if it can be demonstrated that it has the same / similar pharmacokinetic properties to the reference product.

A generic assessed listed product is a medicine that, in comparison to another fully TGA evaluated assessed listed medicine (the "reference product") included in the ARTG:

- a. has the same quantitative composition of therapeutically active substances, being substances of similar quality to those used in the comparison medicine; and
- b. has the same pharmaceutical form; and
- c. is bioequivalent; and
- d. has the same safety and efficacy properties.

All applications for generic systemically acting products must establish bioequivalence between the reference and the proposed products. Bioequivalence refers to the comparability of medicines that are pharmaceutically equivalent and which have no significant difference in the rate and extent to which the active ingredient becomes available at the site of drug action when administered at the same molar dose under similar conditions. Bioequivalent drugs are similar to such a degree that their effects, with respect to both efficacy and safety can be expected to be essentially the same (see [Guidance 15: Biopharmaceutic studies](#)).

Bioequivalence studies should be performed on the **innovator product** (i.e. a product that has had a full efficacy data package evaluated by the TGA), not a generic of the innovator. This is important to reduce the likelihood of **pharmacokinetic drift**, whereby generics that refer to other generics no longer resemble the originally evaluated product due to variability in confidence intervals in each bioequivalence study.

The most reliable means to demonstrate that one formulation will be as effective as another is to conduct a randomised, single-dose crossover bioequivalence study in healthy volunteers. In these studies, subjects receive the different formulations on two separate occasions separated by a wash-out period. A minimum of 12 volunteers, sufficiently long wash-out period (5-7 times the half-life of the drug) to prevent carryover effects, and adequate plasma sampling frequencies should be used. Studies on subjects in the fasted state are usually preferred, as this is the most sensitive condition for detecting differences between formulations. In general, the 90% confidence interval of the ratio of the geometric means of the area under the plasma concentration vs. time curve (AUC) and maximum plasma concentration ( $C_{max}$ ) are required to be between 0.8 and 1.25 for bioequivalence to have been demonstrated.

There are two ways to demonstrate bioequivalence:

1. Where the reference product has previously not been evaluated for bioavailability, bioavailability studies of both the reference and the proposed product are required.
2. Where the reference product has been evaluated for bioavailability by the TGA, similar dissolution profiles between the reference and the proposed products across the physiological pH are taken into consideration to establish bioequivalence.

If the formulations differ significantly and a different release rate has been designed into the formulation, then a non inferiority study against the reference product may be appropriate.

For further information, refer to the TGA-adopted [Guideline on the Investigation of Bioequivalence \(CPMP/EWP/QWP/1401/98 Rev. 1\)](#).

### Generic products that have the same excipients as the reference product

If a product is a generic of an existing product for which bioavailability data exists, and has the same excipient formulation, applicants are able to demonstrate bioavailability by providing:

- a. evidence of identical formulations including excipients;
- b. demonstration of similar dissolution profiles between reference and proposed products across physiological pH; and
- c. scientific justification explaining why points a. and b. above sufficiently demonstrate the bioavailability of the specific product.

Applicants may rely on bioavailability data for an existing product, or data that is obtained through literature, with the appropriate justification. The reference product cannot be a 'grandfathered' medicine.

For further information, please refer to [Guideline on the investigation of bioequivalence](#) and [Guidance 15: Biopharmaceutic studies](#).

### Generic products meeting the requirements for a BCS-based biowaiver

In certain circumstances, despite the product being of a type that would normally require biopharmaceutic studies, it is possible to provide a robust scientific rationale for why bioavailability and/or bioequivalence data might be considered unnecessary for listing of the proposed product. This is generally referred to as a 'biowaiver'.

Biowaivers allow dissolution tests to be used as the surrogate basis for the decision as to whether two products may be considered to be equivalent. In this context, the dissolution and absorption of the medicine is regarded as the critical aspect in determining the equivalence of two products. Consequently, biowaivers are only appropriate for certain classes of products.

The Biopharmaceutics Classification Scheme (BCS) is generally used to determine whether or not a biowaiver may be appropriate. The BCS classifies active substances into four classes based on solubility and permeability, as follows:

	<b>High solubility</b>	<b>Low solubility</b>
<b>High permeability</b>	BCS class I	BCS class II
<b>Low permeability</b>	BCS class III	BCS class IV

Products containing active(s) that are highly soluble, highly permeable (i.e. BCS class I substances) and rapidly dissolving may be considered for a biowaiver. Highly soluble substances are soluble at the highest dose strength in <250 ml water over a pH range of 1 -7.5. Highly permeable substances are those for which the extent of absorption is > 90% of an administered dose based on mass balance or relative to an intravenous reference dose. Rapidly dissolving products are defined as those where no less than 85% of the product dissolves within 30 mins in standard conditions. Excipients that might affect bioavailability should be qualitatively and quantitatively the same in the two products. In general, the use of the same excipients in similar amounts is preferred.

Biowaivers are not usually supported for BCS II –IV substances, or products with more complex formulations such as prolonged release tablets. In some instances, a BCS-based biowaiver may be considered for BCS III products (high solubility, low permeability) where the substance has

high solubility and limited absorption; very rapid *in vitro* dissolution; excipients that might affect bioavailability are qualitatively and quantitatively the same; and other excipients are qualitatively the same and quantitatively very similar.

For additional information about the requirements for demonstrating that a substance can be considered to be BCS class I or III for the purposes of a biowaiver, refer to Appendix III of the TGA-adopted [Guideline on the Investigation of Bioequivalence](#). The [FDA guidance on the BCS](#) may also be helpful.

In all cases, the reference product to which the proposed assessed listed medicine is being compared must have established bioavailability data (e.g. assessed listed or registered medicines, apart from 'grandfathered' products, or products extensively characterised by overseas regulatory authorities). The applicant's justification should address all the aspects of the products outlined in [Guidance 15: Biopharmaceutical studies](#). Additionally, dissolution profiles across physiological pH showing appropriate release of the active(s) must be supplied (this is a standard quality requirement for all medicines).

### 5.5.3 Products not requiring biopharmaceutical studies

For **some L(A)2 and L(A)3 applications**, there is a limited number of products that do not require biopharmaceutical studies, even in the absence of a reference product. These include:

- Aqueous oral solutions that contain the same active substances in the same concentration as a current evaluated product, and that do not contain any excipients that might affect the *in vivo* solubility, *in vivo* stability, gastric passage or absorption of the active ingredient(s). Refer to the [Guideline on the investigation of bioequivalence](#) for more information.
- Oral medicines that are not systemically or locally absorbed (e.g. probiotics, non-digestible polymers, oral suspensions etc.).
- Locally applied products where the active(s) are not systemically or locally absorbed.
- Products with only minor formulation changes - i.e. up to 2% of the total formulation can change compared to the reference formulation, if the change is only to a flavour, fragrance and/or colour (including printing inks). However, you may need to provide dissolution profiles across physiological pH showing appropriate release of the active(s).
- For variations to formulation; medicines with an acceptable correlation between the rate and extent of *in vivo* absorption and the *in vitro* dissolution rate, and where the *in vitro* dissolution rate of the reformulated medicine is equivalent (under the same test conditions used to establish the correlation) to the approved AUST L(A) medicine.

For products that are not systemically or locally absorbed, you may need to provide evidence of non-absorption, and efficacy may need to be demonstrated via clinical studies or other data. Please refer to the relevant guidelines e.g. the [Note for Guidance on the Clinical Requirements for Locally Applied, Locally Acting Products Containing Known Constituents \(CPMP/EWP/239/95 final\)](#).

### Further information

For further information on pharmacokinetic and biopharmaceutical studies, refer to the [Guideline on the investigation of bioequivalence](#).

## 5.6 Justifications

In some cases it might be unfeasible or scientifically unrealistic to supply some required evidence or to meet some of the guidelines mentioned in Sections 4 - 5 above. In such instances, applicants are able to submit a scientific justification (see '[Justification for not complying with technical data requirements or not adhering to guidelines](#)' in the [Mandatory requirements for an effective assessed listed medicine application](#)).

## 6. Alignment of indications and evidence

Regardless of how scientifically sound a study is, its suitability as evidence in support of an application for an assessed listed medicine will depend on how closely the proposed indications for the product match the results and conclusions of the study.

The indications used on a product and the supporting evidence must:

- refer to the same medicine or active ingredient(s);
- have the same meaning and intent; and
- refer to the same therapeutic action and the same context (e.g. the same target population).

Indications must also remain valid for the entire life cycle of the medicine.

### 6.1 Formulation and use

Applicants must ensure that there is a high level of concordance between the study parameters and the product formulation, dosage, and intended target population. The product used in the evidence provided and the product intended for listing should have the same:

- ingredient(s)
- dosage
- dosage form
- route of administration
- frequency and duration of use

If there are differences noted, further evidence and justifications are required to address the data gaps identified (refer to [Biopharmaceutical studies](#)).

Differences in excipients and formulation may be extremely significant. For example, modified release dosage forms of a medicine designed for slow or delayed release of an active ingredient may not be relevant to support indications that imply health outcomes that are achieved rapidly (e.g. 'for the rapid relief of pain').

For traditional use formulations, modifications of the traditional medicine should ensure that the principles of the tradition relating to preparation, constituents and use are followed. If significant modifications are made, these may need to be accounted for through a comprehensive justification.

When evidence relates to a **biological substance** (herb, herbal extract, probiotic, animal-derived product), the species, sub-species, strain, parts, quantity of active component, and preparation **should be identical** to that described in the clinical trial. Given that the chemical profile of any complex substance can vary even if standardised to specific markers, it is unlikely that deviations from the formulation described in a clinical trial will be accepted in these cases.

## 6.2 Duration of studies

Studies must be of an appropriate duration for the indication or claim. The required duration will depend on the nature of the health benefit, but must be sufficient for that benefit to be clearly demonstrated. For example, products that claim a long-term health benefit must be supported by studies of sufficient duration for a sustained response to be apparent. This is particularly critical for indications relating to risk reduction and modulation of biomarkers, as homeostatic mechanisms may reverse changes in the longer term.

Applicants should determine and justify the study duration used to support an indication. Studies of insufficient duration will not be accepted as primary evidence.

## 6.3 Outcomes

Indications should reflect the primary outcome of a study with an adequate sample size. Indications based on secondary outcomes may be acceptable in some cases where these outcomes are statistically and clinically meaningful.

Regardless of the level of the evidence, the indications must not:

- exaggerate the extent, nature, or prominence of the effects achieved in a study; or
- suggest greater scientific certainty than the study is capable of providing; or
- imply efficacy in all instances.

Evidence describing the biological effect, rather than the clinical effect, is not generally a suitable basis for an indication - although it may contribute to establishing the biological plausibility of a proposed primary benefit. This is particularly pertinent in the case of indications that refer to the favourable modulation of biomarkers (e.g. blood glucose levels, cholesterol levels etc.). A small change in a given biological surrogate may be associated with negligible clinical outcomes or increases in risk.

## 6.4 Context

Efficacy studies are usually conducted under tightly controlled conditions in order to control for confounding variables. Studies conducted in this way are ideal for estimating potential efficacy but may not reflect *effectiveness* within its target population e.g. due to different population groups, diets, etc.

Applicants should therefore carefully assess the aspects of the study that were controlled and establish whether the absence of these controls in 'real use' are likely to impact on the benefits experienced by consumers. For example, a study showing a weight loss benefit of a substance may control all participants' caloric intake. Consequently, it is unlikely that the same benefits would be experienced in situations where caloric intake was not controlled.

In such cases, contextual qualifiers should be included in an indication so that it accurately reflects the evidence base. For example:

*'May assist with weight loss when used with calorie controlled diet and exercise'.*

*'May assist with weight management when used with calorie controlled diet and exercise'.*

In situations where real-life effectiveness is likely to be significantly less than that observed in trials, the expected result in the general population should still be clinically meaningful.

## 6.5 Target population and generalisation/extrapolation

For the results of a study to be generalisable to the Australian context, the study used to support the indications for an assessed listed medicine should be conducted using a sample population that:

- consists of both female and male participants
- consists of individuals aged 18-65 years
- consists of healthy, or only mildly unwell, individuals
- is demographically similar to the Australian population

If the indication on the product relates to a **specific population**, then the study should be carried out in that specific population.

Additionally, indications should not extrapolate or generalise the outcomes of a study to populations that differ significantly from that used in the study. Specifically:

- It is not appropriate to use studies carried out on populations with significant health concerns to support an indication for assessed listed medicines; **unless** the indication relates directly to a population with a serious condition (i.e. a restricted representation). If the indication relates to the general healthy Australian population, the extrapolation of study findings from a diseased study population to the healthy Australian population can be misleading. For example, data generated from studies on subjects with biomarker levels outside of normal limits may not be relevant to maintenance of normal biomarker levels in healthy people.
- It is not appropriate to generalise from studies using defined sub-groups to the general population (e.g. it is not appropriate to use a study on 60-65 year old adults to support a claim of efficacy in the general population).
- Similarly, if the study was carried out on a mixed sample population, it is not appropriate to claim efficacy in a select sub-group, unless the study specifically addresses efficacy in that sub-group (e.g. if the study was conducted on a mixed sample of adult women and men, it is not appropriate for the indication to relate to pregnant women).
- The results of a study conducted on a homogenous ethnic population group may not be applicable to the general Australian public, given that the Australian population is culturally and ethnically diverse.

If the target population and the study sample population or sub-group are significantly different, applicants must submit a robust scientific justification accounting for the suitability of the extrapolation (refer to [Justifications](#)).

This justification should consider biological factors as well as environmental and behavioural factors, including the influence of health practitioner intervention which may differ between populations. The mechanism of action of the medicine and whether it is applicable to the population/sub-group should be addressed, given that the same results may not be achievable in other populations or sub-groups due to physiological differences. Further, as any favourable effect is likely to be dose-dependent, consideration should be given to whether the dose requires modification. The justification may use studies on different population groups, non-clinical studies, and *in vitro* studies to support the pivotal study.

## 6.6 Balance of evidence

Indications must not indirectly, or by implication, lead consumers to believe that the medicine will assist in a health benefit that is not explicitly supported by the balance of evidence - i.e. the weight of good quality evidence should be in agreement with the proposed indication. The indication cannot be based on a study that is not consistent with the surrounding body of knowledge (refer to [Balance of evidence and conflicting results](#)).

An indication that is consistent with the broader knowledge base and is supported by the balance of evidence is more likely to remain valid for the life of the medicine as new research becomes available.

## 7. Presentation

The presentation of therapeutic goods is the way in which the goods are presented for supply, and includes matters relating to the name, labelling and packaging of the goods, and any advertising or other informational material associated with the goods.

For example, aspects of the product that are considered to comprise the 'presentation' include:

- the name
- indications
- directions for use
- warning and cautionary statements
- packaging
- dosage form
- logos, symbols and pictures.

Please note that Product Information documents that contain technical information relating to the safe and effective use of a medicine are generally not required for assessed listed medicines, however if included, they may form part of the 'presentation'.

### 7.1 Unacceptable presentation

The presentation of assessed listed medicines is evaluated pre-market. A product will not be approved if the presentation is deemed to be unacceptable. Unacceptable presentation is defined in subsection 3(5) of the Act as follows:

*“the presentation of therapeutic goods is unacceptable if it is capable of being misleading or confusing as to the content or proper use or identification of the goods and, without limiting the previous words in this subsection, the presentation of therapeutic goods is unacceptable:*

- (a) if it states or suggests that the goods have ingredients, components or characteristics that they do not have; or*
- (b) 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*
- (c) if the label of the goods does not declare the presence of a therapeutically active ingredient; or*
- (ca) if the therapeutic goods are medicine included in a class of medicine prescribed by the regulations for the purposes of this paragraph—if the medicine’s label does not contain the advisory statements specified under subsection (5A) in relation to the medicine; or*
- (d) 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; or*
- (e) in prescribed cases.”*

Examples of unacceptable presentations include, but are not limited to:

- therapeutically active ingredients are present in the formulation but not declared as such on the label (and/or misleadingly declared as 'excipients' in the application);
- statements are made attributing a therapeutic role to ingredients that have not been declared as active ingredients, that is: excipient ingredients;
- statements or pictures suggest that the product has uses or actions different from, or in addition to, the indications for use included in the ARTG;
- presentation of a product is in a form likely to result in its being confused with food, for example: in confectionery-like novelty shapes and packaging;
- product names are used that are likely to be misleading as to the composition of the medicine;
- the dosage form or directions are inappropriate for the target population, for example: a capsule dosage form is not appropriate for infants;
- warning or cautionary statements needed for proper usage of the product are omitted;
- claims are made that a formulation is 'hypo-allergenic' or 'non-irritant', unless the sponsor holds supportive evidence from clinical tests that can be produced on request;
- claims are made that a product is free from certain substances, for example: 'free from artificial colours' if not true.

For a detailed outline of many of the considerations for the presentation of medicines, sponsors should refer to [Complementary medicine presentation](#) in the ARGCM. Some considerations for assessed listed medicines are addressed below.

## 7.2 Name

The name of an assessed listed product refers to the identifying descriptor given to the product by the sponsor. This includes a proprietary name; non-proprietary name (e.g. Co-enzyme Q10 100 mg capsules); unique words or codes given to the product; any registered trade mark or other name, mark or logo that uniquely identifies the product; any distinctive colour or label presentation; and generic name (e.g. 'Acme Pharmaceuticals Vitamin C Tablets').

Assessed listed medicine applications will not be approved if, for example:

- the name of a proposed assessed listed product might be misleading as to the composition of the medicine (refer to [Unacceptable presentation](#));
- the name (and any other information on the label) breach the [Therapeutic Goods Advertising Code](#);
- the use of a well-known brand name on new products ('umbrella branding') with different active ingredients relative to existing products, for either the same or a different indication, might cause consumers or health care practitioners to confuse existing and new products.

In instances where a brand name may be acceptable, the name of the new product is assessed based on the extent to which it will be immediately apparent to consumers that they are dealing with a different product. The strength of association of the brand name with the active substance or therapeutic use; the level of differentiation of the presentation of new product relative to current products; and the safety and efficacy in instances where consumers might mistakenly take the wrong product are all considered.

For further guidance, refer to:

- [Current Therapeutic Goods Labelling Orders](#)
- [Therapeutic Goods Advertising Code](#)

## 7.3 Labels

A label, in relation to therapeutic goods, is a display of printed information on or attached to the medicine; on or attached to a container or primary pack in which the medicine is supplied; or supplied with the container or pack.

Medicine labels should comply with all relevant legislation before the medicine can be supplied in Australia, including advertising requirements. Specific documents relating to medicine labelling requirements include:

- [Complementary medicine presentation](#)
- [Therapeutic Goods Regulations 1990](#)
- [Current Therapeutic Goods Labelling Orders](#)
- [Therapeutic Goods Advertising Code](#)
- [Therapeutic Goods \(Permissible Ingredients\) Determination](#)
- [Standard for the Uniform Scheduling of Medicines and Poisons \(SUSMP\)](#)
- [TGA Approved terminology for medicines](#)

Copies of all draft medicine labels must be submitted with all applications to list new medicines and applications to change the labelling of an assessed listed medicine. A certified English translation of any other language appearing on the label must be provided. All text must be consistent with the English information and not include or imply any additional indications.

During the evaluation, all aspects of the medicine presentation, including proposed labelling and package inserts (if present), are assessed for compliance with the various legislative requirements (including advertising requirements). Some points of particular note are outlined below.

### 7.3.1 Listing number

Once approved, assessed listed medicines are assigned a unique AUST L(A) number which must be displayed on the label in accordance with the requirements of the [Therapeutic Goods Labelling Orders](#) and the *Therapeutic Goods Regulations 1990*.

### 7.3.2 Ingredients

The [Therapeutic Goods Labelling Order](#) specifies how ingredients should be declared on labels, and specifies the disclosure of certain excipients.

An excipient ingredient need not be nominated on a medicine label, unless it is a restricted ingredient (i.e. subject to a quantity or concentration based restriction referred to in a legislative instrument, such as the [Therapeutic Goods \(Permissible Ingredients\) Determination](#)). Where a sponsor chooses to disclose a (non-mandatory) excipient on a medicine label, then all excipients must be disclosed – i.e. declaration of excipients on a medicine label cannot be selective.

Statements such as 'gluten free' or 'sugar free' must be true of all ingredients in the medicine, including proprietary ingredients. The sponsor should provide written assurance in their submission that the product does not include the stated substance.

If the formulation includes a proprietary ingredient, the sponsor should check with the manufacturer or supplier of the proprietary ingredient to ascertain that it does not contain any component it is claimed to be 'free of' on the label. The sponsor should also check whether the proprietary ingredient contains any specified excipient that must be declared on the labels in accordance with the Labelling Order and the Therapeutic Goods (Permissible Ingredients) Determination.

Claims relating to excipients will be assessed by the TGA during the evaluation.



In order to comply with their statutory obligations, sponsors are required to have evidence that their products do not contain undeclared declarable excipients, and do not contain ingredients they are claimed to not contain. This includes components of proprietary ingredients.

### 7.3.3 Directions for use

Directions for use of assessed listed medicines include the following information for each target population for which the product is intended:

- dosage
- method of administration
- frequency and duration of treatment for each indication
- relevant target population (e.g. age), where applicable.

For liquid products, recommended doses should be able to be measured using commonly available metric measures, or a suitable measure provided in the pack. References to a culinary 'spoonful' (e.g. teaspoon, dessertspoon, tablespoon, etc.) are not acceptable.

Products which are intended for symptomatic relief should include a qualifier such as 'as required' or 'when necessary' after the specific dosage frequency (e.g. 'take one tablet in the morning when necessary'). The directions 'as required' or 'when necessary' are not acceptable on their own.

A statement regarding 'duration of use' should be included on the label.

### 7.3.4 Claims

Claims that do not include a specific therapeutic use of the medicine (e.g. 'contains 30% more', 'water resistant' etc.) are not considered to be indications. Such claims are not required to be in the ARTG entry for a medicine.

However, the medicine label must not include any claim that is inconsistent with the information included in the ARTG for the medicine, and must comply with applicable standards and advertising requirements outlined in [Complementary medicine presentation](#) and the [Therapeutics Goods Advertising Code](#).

Label flashes such as 'New Formulation' or 'Now with ...' should not be used to describe any product, presentation, indication or claim which has been available and promoted in Australia for more than 12 months.

The product labels and all claims are pre-market assessed by the TGA. Sponsors of assessed listed medicines must therefore provide evidence at the time of application to support all claims for the formulated product. Some types of claims have specific requirements, as outlined below.

### Claim that product has undergone efficacy assessment



As part of the Government's complementary medicine's reforms, the TGA is considering a 'claimer' to allow assessed listed medicines to claim that the product has undergone efficacy assessment. The TGA is refining options for the claimer after receiving comments from consumers and industry during the public consultation process.

### Claims implying a high level of certainty

Claims that may lead consumers to believe that the evidence supporting the efficacy of a product is unequivocal are not appropriate unless supported by sound data from robust clinical trials on the product. This includes graphics or flashes using text such as 'clinically' and 'scientifically' in combination with 'proven', 'tested', 'trials' etc.

### Claims of rapid effect

Claims of 'fast' or 'rapid' action or effect may be used when the indications are for relief of symptoms where the speed of onset is relevant and they are well supported by **clinical** and **pharmacokinetic** data. They are not suitable when used in relation to chronic conditions, conditions not requiring immediate relief, or medicines where the pharmacokinetics or mechanism of action precludes a fast action. For further information, refer to [Guidelines on presentation aspects of OTC applications](#).

### 7.3.5 Warning and disclosure statements

Product labels must include the advisory statements required by the [Therapeutic Goods \(Permissible Ingredients\) Determination](#) and [Standard for the Uniform Scheduling of Medicines and Poisons \(SUSMP\)](#). These legislative instruments work in conjunction to regulate ingredients included in all listed medicines, as described in Item 3 of Schedule 4 to the *Therapeutic Goods Regulations 1990*. As a result, if a requirement is included in the SUSMP, it applies to listed medicines, even if that requirement is not expressly stated in Therapeutic Goods (Permissible Ingredients) Determination.



All indications relating to symptoms must be accompanied by the statement 'If symptoms persist consult your healthcare practitioner' or words to that effect.

The TGA may request the inclusion of other warning statements and/or contraindications on the product label and/or package insert during evaluation of an application to list or vary a product.

### 7.3.6 Comparisons, endorsements and sponsorships

Statements comparing a product with other products or treatments must be supported by acceptable evidence, and must comply with the [Therapeutic Goods Advertising Code](#).

Labels must not contain or imply endorsement of the product, except as permitted by the Advertising Code. Once an endorsement is no longer applicable, the sponsor must remove the endorsement via a notification to the TGA.

Labels may include reference to sponsorship of the product when in compliance with the Advertising Code. Sponsors should provide evidence that claims relating to any such sponsorship are true, for example, a letter from the relevant organisation showing that claims relating to any such sponsorship are true.

Where the sponsorship includes a potential restricted representation, a request for approval of the restricted representation must be included in the medicine application.

### 7.3.7 References to internet sites or other products

The inclusion of internet addresses on labelling is only acceptable where the information on the website (including any direct links from that website) is consistent with the information included in the ARTG for that product. Websites are considered advertising and are subject to the [Therapeutic Goods Advertising Code](#).

References to a sponsor's other products may be permitted, provided that the products are included in the ARTG and have been pre-market assessed for efficacy. This includes situations where reference is made to:

- more suitable dosage forms within the same range for different age groups
- another product that can be used in conjunction with the product, where appropriate
- other products within the same product range that have the same trade name as the current product, where appropriate.

### 7.3.8 Graphics, logos, symbols and market differentiations

Non-corporate graphics, logos or symbols on labels must be consistent with the product's approved details, including being appropriate for the claimed therapeutic use of the product. For example, a graphic highlighting joints would be inappropriate for a product that is indicated for use only on soft tissues.

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 (see [Unacceptable presentation](#)).

## 7.4 Advertising

An advertisement, in relation to a therapeutic good, includes any statement, pictorial representation or design, however made, that is intended, whether directly or indirectly, to promote the use or supply of the goods.

All adverts for assessed listed medicines, including all Australian-based websites promoting the supply or use of therapeutic products, must comply with in Part 5-1 of the Act and the [Therapeutic Goods Advertising Code](#).

### 7.4.1 Restricted representations

It is both an offence under the Act (see paragraph 42DL(1)(c)) and a breach of the Therapeutic Goods Advertising Code for a sponsor to refer to a restricted representation without **prior approval** of the Secretary of the Department of Health.

To obtain approval for the use of a restricted representation in relation to an assessed listed medicine, sponsors may submit a request under section 42DE of the Act at the time of application for the listing of the medicine. The '[Application for approval to use a restricted representation in advertising](#)' on the TGA website should be included in the evidence package submitted to the TGA, and should be supported by scientific evidence appropriate for an intermediate level indication. The application must also provide a justification as to why the representation is necessary for the appropriate use of the medicine and how the public interest criteria will be applied (see [Therapeutic Goods Advertising Code](#)).

## 8. Application dossier requirements

The application dossier<sup>17</sup> for listed medicines is based on a simplified version of the CTD structure. This structure allows evaluators to quickly and efficiently locate specific information.

All application dossiers must consist of the following components:

- Application form
- [CTD Module 1: Administrative information for assessed listed medicines](#) including cover letter.

L(A)2 and L(A)3 applications must also include any additional documents specified in the [Mandatory requirements for an assessed listed medicine application to pass preliminary assessment](#).

The dossier must adhere to the TGA's [general dossier requirements](#) and the CTD module-specific guidelines.

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<sup>17</sup> The definition of a dossier is: "A collection of files and documents that contains data (administrative, quality, nonclinical and clinical) relating to a therapeutic good."

## 9. Application and approval processes

All medicine applications that involve pre-market assessment by the Complementary and Over the Counter Medicines Branch (COMB) follow a similar sequence of processes. The main difference between applications of different types is that applications in lower categories have shorter assessment timeframes due to the reduction in information to be evaluated. The steps involved in most applications are:

1. [Pre-submission](#)
2. [Submission](#)
3. [Preliminary assessment](#)
4. [Evaluation and requests for information](#)
5. [Decision](#)
6. [Finalisation](#)
7. [Post-listing](#)

The sections below provide further information on each of these steps.

### 9.1 Pre-submission

#### 9.1.1 Verifying eligibility and validity

Before submitting an application, potential sponsors should ensure that the proposed product meets the [eligibility requirements](#) for the assessed listed medicines pathway.

#### Checking ingredients

All ingredients (active and excipients) must be included in the latest [Therapeutic Goods \(Permissible Ingredients\) Determination](#) and the formulation must be compliant with any restrictions or requirements associated with those ingredients.

If the product contains any ingredient not specified in the Determination, applicants will need to submit an application for a new substance for use in listed medicines prior to proceeding, or alternatively submit an application for a registered complementary medicine.

If the medicine contains any proprietary ingredients (PIs) - including flavours, fragrances and printing inks - applicants will need the proprietary ingredient ID number. PIs are listed in the [Proprietary Ingredients Table](#). If the PIs are new (i.e. not in the Code tables), applicants must submit the completed [Notification of a Proprietary Ingredient form](#) to obtain a PI ID number.

New PIs intended for use in listed medicines must only contain ingredients specified in the [Therapeutic Goods \(Permissible Ingredients\) Determination](#). If this is not the case, applicants will need to submit an application for a new substance for use in listed medicines. Note that the application for an assessed listed medicine cannot proceed until the ingredient has been successfully evaluated and added to the Determination. This may cover a significant period of time.



All substances in a PI intended for use in listed medicines must be included in the Therapeutic Goods (Permissible Ingredients) Determination. It is the sponsor's responsibility to confirm that the PI does not contain any ingredients not on the Determination, and that warning statements related to any PI components that need to be declared are included on the label.

## Checking the indications and claims

Applicants must ensure that the indications and claims on the label are appropriate for the assessed listed medicines pathway and that they correctly align with the evidence supplied in the application. This includes ensuring that the formulations, dosage, route of administration, and target populations are all substantially similar to those employed in the studies. If the indications or claims include restricted representations, a request for approval of the representation must be included in the application (see [Advertising – Restricted representations](#)).

## Checking evidence

Applicants should check the minimum data requirements for the method by which they intend to support the efficacy claims. For an application to be considered to be effective, it must contain the correct type, number and quality of studies; the correct type of pharmacokinetic/biopharmaceutical studies; and GMP clearance valid for the entire duration of evaluation. If the GMP clearance is due to expire within the minimum timeframe or is likely to expire before the application is finalised, applicants should either apply to renew the GMP clearance or seek an extension to the GMP clearance expiry before submitting the application.

It is recommended that applicants check all of the relevant [European Union and ICH guidelines adopted in Australia](#) for any specific requirements that may apply.

## Label proofs

Proofs of the proposed labels must be submitted. The labels should comply with the relevant [Therapeutic Goods Orders](#) and must include at least one intermediate level indication. All indications and claims on the label will be assessed by the TGA. Only assessed indications will be included in the ARTG entry for the product if it is approved.

### 9.1.2 Determining the application category and compiling the dossier

There are three categories for applicants to list medicines based on risk, with L(A)1 being the lowest and category L(A)3 being the highest risk. The data requirements and [timeframes](#) increase with the level of assessment and risk mitigation required.

It is important that applicants determine the application category correctly. If the application does not meet the requirements of the selected category, and does not include the required data, it will not be accepted for evaluation. To help determine the correct application category, refer to [Application categories for assessed listed medicines](#).

The assessed listed medicines pathway uses a simplified version of the CTD format for organisation of evidence. The application should be prepared following the [Application dossier requirements](#).

### 9.1.3 Pre-submission meeting

Applicants can arrange a free optional [pre-submission meeting](#) with the TGA prior to submitting the application for a new assessed listed medicine.

Pre-submission meetings are not mandatory but are strongly recommended. They provide an opportunity for applicants to seek clarification of the requirements and to revise the approach to their application. These meetings may help applicants submit a high quality and complete dossier, and consequently ensure that the evaluation process proceeds smoothly and in line with legislated timeframes.

During the pre-submission meeting, discussion will focus on the structure of the proposed application, the identification of critical issues and the suitability of the proposed approach. The TGA does not assess or evaluate the application as part of a pre-submission meeting.

After the meeting, the applicant forwards minutes of the meeting to the TGA and any other participants. If necessary, the final meeting record should be included in Module 1 of the application dossier.

To arrange a free meeting with the TGA, follow the [general guidance on pre-submission meetings](#).

## 9.2 Application submission

### 9.2.1 Completing and submitting the application

Applications are created and lodged through [TGA Business services](#). Applicants will need a Client ID number and a password access to the TGA Business services. Applicants who do not have a Client ID number or access to TGA business services should submit the online [organisation details form](#).

The [Guidance for completing the application form for an assessed listed medicine](#) provides instructions on completing the application form for the listing of the assessed listed medicine.

Once the application has been submitted, applicants will be issued with a unique submission number that can be used in all future communications about the application.

### Withdrawing an application

An application can be withdrawn at any time up until the decision is made. This can be done through the Business Services. Alternatively, applicants can advise the TGA in writing of the intention to withdraw the application.



When an application is withdrawn, the TGA may retain the application and any material submitted in connection with the application.

### 9.2.2 Application fee payment

Once an application has been received by the TGA, an invoice will be issued for the application fee. For details of the current fees, refer to [Schedule of fees and charges](#).

For information on fees and the available payment methods see:

- [Fees & payments](#)
- [Payment options](#)



The TGA will not commence screening the application until the application fee has been paid.

## 9.3 Preliminary assessment

The TGA will conduct a preliminary assessment of the application to determine whether it meets the administrative requirements and basic technical eligibility requirements (e.g. correct application type and application fee, and adherence to the [Mandatory requirements for an assessed listed medicine application to pass preliminary assessment, CTD Module 1: Administrative information for assessed listed medicines](#) and [General dossier requirements](#)) to proceed to evaluation. This is simply a quality assurance process, and no evaluation of the scientific content of the application is undertaken at this point.

### 9.3.1 Applications that pass preliminary assessment

The application will pass preliminary assessment if it meets the requirements under section 23B of the [Act](#). Generally, this means that:

- the prescribed application fee has been paid; and
- the application includes all required information, for the correct application category, to enable the TGA to evaluate the application.

Applicants will have an opportunity to make minor corrections detected during the screening process if the issue can be rectified promptly. For example, if the evaluators cannot locate an attachment mentioned in the application, the TGA will provide an opportunity to submit the attachment.

If the application passes preliminary assessment, the applicant will be notified in writing that the application has been accepted for evaluation and an invoice will be issued for the evaluation fee. The evaluation process will not commence until the evaluation fee has been paid in full.

### 9.3.2 Applications that do not pass preliminary assessment

If the application does not pass preliminary assessment, it will not be accepted for evaluation. The applicant will be notified in writing and an explanation of why the application was not effective will be provided. The application fee will not be refunded. Applicants are not able to appeal this decision under section 60 of the Act.

If you reapply to list the medicine on the ARTG, ensure your application meets the requirements for an effective application.

You cannot lawfully import, supply or export the medicine until you have an ARTG listing.

### 9.3.3 Lapsing applications

The application will lapse if evaluation fees are not paid within 28 days of becoming payable. The TGA will notify the applicant of the lapsing of the application. A new application must be submitted, and a new application fee paid, if the applicant wishes to list the medicine.

## 9.4 Evaluation and requests for information

Once an application has passed preliminary assessment and the evaluation fee has been paid, it enters the evaluation phase. During this phase, the TGA assesses the application, reviews any responses to requests for information, and documents the findings.

## 9.4.1 Evaluation

The TGA assesses the efficacy data to determine whether it supports the indication(s)/claim(s); and the product label. The assessment includes:

- a review of the types, quantity, quality and validity of studies;
- a detailed evaluation of the proposed indication(s) and claim(s);
- assessment of the medicine presentation for compliance with the various legislative requirements (including labelling and advertising requirements).

## 9.4.2 Requests for information (RFIs)

The TGA may make a request under section 31 of the Act for additional information to clarify or address issues identified during evaluation. During this time, the evaluation clock will stop. However, evaluators may also seek clarification of minor issues on an informal basis. The clock will not stop in these circumstances.

The applicant should provide an electronic copy of the requested information. No additional unsolicited data will be accepted.

Applicants will be notified of the timeframe for the response. It is important that applicants respond to an RFI within the timeframe provided. If the response is not received within the timeframe specified, or if the issues identified in the RFI remain unaddressed, the application will proceed to the decision phase without the additional information. This may result in the rejection of the application.

Although the TGA may grant extensions to the RFI due date, this will only be done at the discretion of the delegate if the request is received well before the due date, and if the applicant provides a reasonable justification as to why the extension is necessary.

The time between the RFI being issued and receipt by the TGA of the applicant's response will not be counted as part of the evaluation timeframe (i.e. the 'evaluation clock' will stop).

## 9.4.3 Expert advisory committee advice

The TGA may decide to seek advice from an [expert advisory committee](#), such as the [Advisory Committee for Complementary Medicines \(ACCM\)](#). The TGA will notify applicants of the date of the committee meeting and provide an opportunity for a submission for the committee's consideration. Any advice received from the committee will be communicated to the applicant.

## 9.5 The decision

When making the decision under section 26AE of the Act on whether to list the medicine in the ARTG, the decision maker (the delegate of the Secretary of the Department of Health) will review all documentation associated with the application, including the dossier, evaluation reports, responses to requests for information, and advice from expert advisory committees.

### 9.5.1 Decision to list the medicine

If the delegate considers the efficacy of the medicine to have been established and makes a decision to approve the listing of the medicine, the TGA will notify the applicant in writing of the decision.

The decision letter will outline standard and specific conditions on the listing of the medicine under section 28 of the Act. It is important that applicants read, understand and comply with

these conditions. If the sponsor does not comply with any one of these conditions of listing, the medicine may be cancelled from the ARTG.

The decision letter will request that the sponsor provides assurance that all details of the medicine are correct before the ARTG entry is created.

### 9.5.2 Decision not to list the medicine

If the decision is not to list the medicine, the decision letter will include a statement of the reasons for the decision and information on the applicant's rights to seek a review of the decision. Applicants are able to appeal this decision under section 60 of the Act.

## 9.6 Finalisation

### 9.6.1 Patent certification under the Australia / USA free trade agreement

Sponsors need to provide a [patent certificate under subsection 26B\(1\) of the Act](#), or notification that this is not required before the medicine can be listed in the ARTG.

If this was not provided with the application, one of the following documents should be completed and submitted via email to [complementary.medicines@health.gov.au](mailto:complementary.medicines@health.gov.au), quoting the submission number:

- [approved form for notification that 26B\(1\) certificate is not required](#)
- [approved subsection 26B\(1\)\(a\) or \(b\) certificate](#).

### 9.6.2 Listing the medicine

Once the completed and signed notification form or patent certificate has been received, the TGA will list the medicine in the ARTG and the product will receive a unique AUST L(A) number.

Sponsors are able to download the certificate of listing from Business Services. To do this, follow the [guidance on printing an ARTG certificate](#). The listing of the medicine will commence on the day specified in the certificate of listing. The medicine cannot be lawfully imported, exported or supplied by the applicant prior to this date.



The product details will usually be viewable on the [TGA Business Services website](#) the day after the information has been recorded in the ARTG.

## 9.7 Post-listing

### 9.7.1 Publication of outcomes

The TGA may choose to publish a notification of the approval of the medicine on the TGA website. This notification may include the name of the medicine, the sponsor, the approved indications, and any other supporting information necessary. No confidential information (e.g. trade secrets) will be published.

[Notices of restricted representations approved under section 42DF and 42DK of the Act](#) are published on the TGA website.

### 9.7.2 Annual charges

Annual charges will apply to all medicines included in the ARTG.

The charge is applied on an annual basis (in July of each year for existing entries in the ARTG) or upon listing of the goods in the ARTG during a financial year). The annual charges apply to any product in the ARTG at any time during a financial year, regardless of whether the product is subsequently cancelled within the same financial year.

Any new product entering the ARTG will qualify for an annual charge exemption (ACE) until such time as the product generates turnover (refer to [Annual Charge Exemption Scheme](#)).

### 9.7.3 Post-market compliance

Assessed listed medicines, like all listed medicines, may be selected for a post-market compliance review at any time. The TGA will check the assessed listed medicine's compliance against the regulatory requirements that are self-certified by the sponsor. Efficacy of the product will not be routinely reviewed post-market.

If an assessed listed medicine is selected for a compliance review, a request for specific information under section 31 of the Act will be issued by the TGA to the sponsor. Sponsors will generally have 20 working days to respond. It is an offence to fail to respond to the notice or to provide information that is false or misleading in a material particular. Failure to provide the information by the date specified in the notice is grounds for cancelling the medicine from the ARTG.

For more information refer to [Listed medicine compliance reviews](#).

Assessed listed medicines must also comply with any standard and specific conditions applying to listed therapeutic goods under Section 28 of the Act.

## 10. Timeframes and fees

### Timeframes

The TGA has established statutory evaluation timeframes for pre-market evaluation of products submitted under section 26AE of the Act (assessed listed medicines). These are provided below.

**Table 9: Timeframes for the evaluation of assessed listed medicines**

Application category	Notification of preliminary assessment (working days)	Evaluation timeframe (working days)
L(A)1	40	45
L(A)2	40	60
L(A)3	40	150

The above evaluation timeframes:

- apply to **working days** only, and exclude public holidays and weekends;
- exclude where the evaluation clock has stopped e.g.
  - for the time taken by the applicant to provide responses to formal requests for information made by the Secretary under section 31;
  - when the applicant and TGA agree to a mutual stop clock.
- only commence once an application has been accepted for evaluation and following payment of the evaluation fee. The delegate of the Secretary will notify an applicant in writing within 40 working days of receiving the application whether the application has passed preliminary assessment; and

Although the TGA is required to complete the assessment within the specified timeframes, applicants should not presuppose the outcome of an application. The Commonwealth and its representatives are not liable to a person for loss, damage or injury of any kind that is caused by or arises from a failure to decide an application within the specified timeframe.

### Fees

The fee structure aligns with the application categories and associated evaluation workload. There are two components to the fees for an application - an administrative application fee, and an evaluation fee.

- The application fee cannot be waived, reduced or refunded.
- If the application is withdrawn before it enters the evaluation step in the process, the evaluation fee will be refunded. The application fee will not be refunded.
- In exceptional circumstances, the Secretary may waive or reduce an evaluation fee if there is information to enable an evaluation to be abridged.

## Version history

Version	Description of change	Author	Effective date
V1.0	Original publication	Complementary and OTC Medicines Branch, TGA	March 2018
V1.1	<p>Modified evidence for low level indications, consistent with listed medicines evidence requirements. Removed cross-references to guidelines to avoid confusion.</p> <p>Additional information on biopharmaceutic studies and biowaivers.</p> <p>Clarified use of CORs.</p> <p>Included cross-reference to 'Guidance for completing the application form for an assessed listed medicine'.</p> <p>Amended pre-submission meeting process.</p> <p>Corrected appeal of preliminary assessment decisions and timeframe for lapsing applications.</p> <p>Other minor amendments.</p>	Complementary and OTC Medicines Branch, TGA	August 2018

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