Member Alert

IMPROVED & UPDATED: Assessed Listed Medicines Evidence Guidelines

The TGA has published an updated version of the Assessed Listed Medicine Evidence Guidelines following an internal TGA review of the AUST L(A) evidence guidelines throughout 2023-24. Whilst the TGA were originally planning an administrative update only, CMA has strongly advocated for further updates to scientific expectations and clarity of the requirements to provide industry greater confidence in the pathway.

Notable updates to the guidelines that are seen to improve industry's use of the pathway include:

- **Large improvements to scientific interpretations including broader approaches to study methods and analysis/assessment;**
- **Literature-based submissions: removal of resource intensive and unrealistic requirements;**
- **Reorganisation and condensation of technical information;**
- **Improved clarity and reduction of technical language, resulting in a more user-friendly document.**

The cumulative effect of the changes to the document means that the updated 2024 version of the guidelines is significantly easier to understand for applicants, and importantly, has scientific parameters that are easier to seek an application for, for both clinical trial based applications and literature-only applications.

Greater use of the AUST L(A) pathway opportunity is expected to:

- Expand the therapeutic horizons and increase the specificity of complementary medicine indications
- Increase consumer and medical confidence in the evidence and health claims
- Increase Australia's recognition as a world-class industry and a leading regulatory system
- Increase sales of Australian products domestically and globally, and stimulate new innovation and research.
- Encourage increased Government research funding as increased efficacy claims are publicly recognised.

This member alert provides information for members on updates to the AUST L(A) guidelines, including improvements, reduced barriers, and areas that CMA consider are likely to require further review.

CMA has secured speakers from the TGA to attend CMA's 7 May Innovation Day to introduce changes to the AUST L(A) evidence guidelines and answer industry questions.

Be sure to secure your place at Innovation Day by registering for the event here.
Register your AUST L(A) questions for TGA ASAP to technical@cmaustralia.org.au

The review of the AUST L(A) evidence guidelines occurred in collaboration with CMA and our Scientific Advisory Working Group. CMA identified a number of areas where future policy changes are required if the pathway is to achieve its initial intentions of consumer benefit and industry expansion. The TGA provide that a number of changes requested by CMA

have been implemented. The update has also taken into consideration advice from the Advisory Committee of Complementary Medicines (ACCM), and the TGA's experience with AUST L(A) applications received to date.

The TGA have acknowledged that, because the update needed to be published quickly to reflect administrative updates, there are areas of the guidelines that require further consideration, which will be subject to ongoing discussion with CMA and may be addressed in future updates to ensure the guidelines are as comprehensive and effective as possible.

CMA will continue to advocate for improvements to the AUST L(A) pathway to increase the evidence base for complementary medicines, increase recognition of Australian products, increase market share for assessed medicines, and ensure the ongoing growth of our unique academic sector.

Members are invited to provide feedback to CMA on the updated V1.2 guidelines and desirable future updates via technical@cmaustralia.org.au

Reduction in barriers

CMA consider the updated version (V.1.2) of the Aust L(A) Evidence Guidelines to be a clearer more user-friendly version with requirements better articulated, and some barriers removed. The adopted changes indicate a better appreciation of industry perspectives, reflecting a shift to a more industry sensitive position on requirements. Important clarifications that are a positive step in reducing barriers for sponsors to make applications are summarised below.

Literature-based Submissions More Accessible

A literature-based submission has become a more realistic option in the updated 2024 Guidance, with **the removal of the requirement that applicants secure access to the raw data behind any peer-reviewed published trial** included in the submission. CMA considered this expectation to be unrealistic, inequitable, and burdensome, and emphasised that there is no such requirement in the Registered medicine pathway. Further, such material can be difficult to access due to time constraints and cannot be accessed without permission.

Other changes in wording may also improve sponsor's confidence in using the literature-based route. For example, **Table 5 (page 23) clarifies that a Literature search report demonstrating the body of scientific knowledge is permitted**.

CMA consider further clarification is required around efficacy evaluation and TGA expectations of good quality clinical trial design and reporting, including minor protocol changes. We will draw further attention to these aspects at the next review, however, in the interim CMA reminds members that robust scientific advocacy for the plausibility of an indication based upon the available evidence is often a path to a successful application with the TGA.

Modifications in Approach to Analysis: Per-Protocol Analysis now Accepted

Per-Protocol (PP) analysis is now acknowledged as an alternative to Intention-to- treat (ITT), contingent on the specifics of the research question, study design etc. Per-protocol analysis can be utilised alongside ITT *or* in lieu of it. This is significant outcome for Assessed Listed medicines since, it is harder to demonstrate efficacy using an ITT analysis, especially with small numbers of participants typical of CM clinical trials. **Employing PP analysis is commensurate with the low risks of the ingredients included in proposed AUST L(A) medicines. This clarification may also improve the success of literature-based submissions, since PP analysis of clinical trials is common** (p.55).

Clinical Significance Assessments Broadened

Another change in emphasis with potentially important implications is **the acknowledgment that there are many approaches to assessing clinical significance**. This is critical to complementary medicines, as many trials are carried out in healthy populations where reliably measuring clinical significance is challenging. Note that the guidelines require the assessment method be determined *a priori* and to relate clearly to the expected clinical benefit.

Study Methods Broadened

While human studies remain the foundation evidence for intermediate level indications (at least one of which is required to apply for a listed assessed medicine), the updated guidelines provide important clarification about the role other types of studies may play in an AUST L(A) application. **Evidence provided by non-human and *in vitro* studies can be used to extrapolate biological plausibility and support use in the intended target population. Likewise, these study types can provide evidence of a biopharmaceutic and pharmacokinetic activity.** See for example the Information box in Section 5 (page 28).

Prediction of Clinical Benefit and Long-Term Benefits permitted

Another significant change, advocated for by CMA, was to align the requirements of the Assessed Listed pathway more closely with those for OTC and prescription medicines regarding evidence to support the long-term benefits of AUST L(A) medicines. The latest guidelines make it clear that **extrapolations from "epidemiological studies, other clinical trials on similar products, and a discussion on physiological mechanisms to demonstrate biological plausibility" (page 35) can all be used in a justification for long-term benefits**.

A key clarification for sponsors wishing to provide evidence **for intermediate indications focused on prevention or risk reduction, is the acknowledgement that justifications can be supported by evidence based on biological surrogates, including some biomarkers, to predict clinical benefit**.

Secondary Outcomes Acceptable for an Indication when the Primary Endpoint is Acceptable

CMA advocated that it is scientifically correct to accept secondary outcomes as valid due to the nature of clinical research. The TGA have clarified that **indications based on secondary outcomes which are both statistically and clinically meaningful may be acceptable evidence to support a new indication**. This is qualified later in Section 10 Appendix and at this stage will only apply when the primary endpoint is statistically significant. CMA may return to this during ongoing guidelines review based on Scientific Advisory Working Group advice.

Evaluation Expectations Clearer

The TGA has provided applicants with increased information about how their submissions will be evaluated, by including links to a **TGA-adopted EU guidance document that covers submissions based on one pivotal study**. Another important change is the reference to the Grading of Recommendations Assessment Development and Evaluation (GRADE). This tool allows industry to assess the strengths and weaknesses of the collected evidence to support an application and acknowledges that evidence does not have to be perfect to be valuable.

Herbal ingredients

There has been some clarification in the section concerning the alignment of herbal medicines included in formulations with those used in scientific trials. Applicants may include a herbal preparation in a formulation that differs in some

specified parameters from a clinically trialled herb. However, a robust justification is required to account for disparities between the characteristics of the herb included in proposed AUST L(A) medicines and the trialled form.

The issue of demonstrating bioequivalence remains a complex one, but the section has been reworded to provide a way forward. CMA will continue to work on proposals for the development of reasonable guiding principles when considering formulations and equivalency of herbal medicines to improve the valid and reasonable use of the pathway for potentially clinically valuable products. As this is a complex area, CMA welcomes member feedback on work that has already been done in this space or valuable international examples.

Label Presentation – Duration of Use; Graphics, Logos, and Symbols

CMA identified inconsistency regarding labelling obligations, which has been addressed in the current guidelines. Specifically, AUST L(A) labels no longer need to include information about the duration of use unless it specifically pertains to safety or efficacy. Additionally, the latest guidelines clarify that it is acceptable to incorporate non-corporate graphics, logos, and symbols on new AUST L(A) product labels, provided they align with the product's approved information (ARTG) and are distinguishable from existing products. Further, advertising is permitted to include supplementary information beyond what is listed in the ARTG, as long as it remains consistent (refer to Sections 7.3.8 and 7.1 for more details).

Technical improvements

Details about clinical trial methodology, analysis and reporting have been moved from Section 5 into an Appendix in section 10, so that the technicalities no longer interfere with understanding the key definitions and processes. The Appendix also includes links to a number of TGA-adopted EU guidelines and other tools to assist with the design and in the quality appraisal of clinical trials, including EMA Guidelines and the Cochrane Risk of Bias Tool.

A great deal of redundancy has been removed and links to appropriate detailed guidance from the TGA are included instead. The document is easier to understand while improvements in language and inflection, like the substitution of ''should'' for ''must'', makes the Guidelines more approachable for applicants seeking a successful outcome.

Application and approval processes (Section 8) has also been improved in response to CMA feedback. This section pulls together information about details of the pathway covered in earlier sections, and describes the process of putting together and submitting the application. A number of minor changes improve clarity and readability. For example, an extra information box (in section 8.1.2) flags to sponsors that indication(s) to be evaluated by the TGA in the application dossier, on the label and on the ARTG, should be consistent. The previous confusion over the wording of indications has likely resulted in delays.

CMA received feedback from members that TGA references to indications based on traditional use caused confusion as intermediate indications can only be based on scientific evidence. This has been rectified in the updated version. Note that low-level permitted indications proposed for AUST L(A) medicines may be included in an application and while they also need to be based on scientific evidence, reference can be made to use in a traditional context (page 28). In the previous 2018 guidelines the terms therapeutic indication and intermediate indication were used interchangeably which also caused confusion. In the updated version, the term 'intermediate indication' is defined and used consistently. In addition, information about the data protection scheme is included in these guidelines. This scheme was introduced too late to be included in the first version of the guidelines.

Pre-submission Meetings

Details regarding pre-submission meetings are clearer. This is an optional meeting requested by the sponsor and has no fees associated with it. It provides an opportunity for a sponsor to ask questions and potentially improve or complete their dossier before the application is submitted. Sometimes questions can be worked through in writing, in which case, no meeting is needed. Where a meeting occurs, sponsors share a summary or record of the meeting with the TGA to ensure both parties are clear on agreed outcomes and any actions arising and the TGA will acknowledge receipt of the meeting record.

Fee process clarified – lower cost if applications do not proceed to evaluation.

It is now clearer that fees are required at two timepoints in the submission process: firstly, there is an application fee, payable when the application is submitted to cover the preliminary assessment which ensures the application has the data elements that are expected to be able to proceed to evaluation. The TGA notifies sponsors once an application has passed this preliminary hurdle, and at this point, the Evaluation fee is to be paid before the evaluation starts.

Areas CMA consider the AUST L(A) guidelines would benefit from further review

CMA raised a number of issues with the TGA during the 2023-24 review of the guidelines that have not been addressed due to timeframe limitations for releasing the administrative changes. CMA has additional complex issues that we need to research further for proposing changes, such as herbal bioequivalency. CMA will address these aspects again in the context of an ongoing review to improve the guidelines. These aspects are summarised below.

Industry relevant and risk commensurate evidence requirements

CMA have identified a number of areas in which the AUSTL (A) pathway refers to standards that are not desirable for complementary medicine, but rather to applications for prescription medicines. CMA have questioned the relevance of this data in the context of complementary medicines and recommend that the policy review include biopharmaceutic and pharmacokinetic studies which include immediate release and modified release oral dose forms. CMA has also identified concerns with the section on Generic products, as some standards appear to be taken from requirements for prescription medicines and are not necessarily applicable to complementary medicines. For example, dissolution profiles are not possible for all complementary medicine products.

Permitted differences in L(A) applications

CMA consider some requirements of the L(A)1 category, which covers minor changes to existing assessed listed medicines, are unnecessarily restrictive, including restrictions on flavours, fragrances and/or colours and pack sizes.

Improved access to AUST L(A) for complex chemical substances including herbal extracts

CMA consider the current methods of establishing efficacy require further review to address requirements for establishing 'substantial similarity' of complex herbal or other substances. CMA intend to propose an amendment to existing methods, or development of a new method, to assist sponsors seeking to introduce products based on herbal extracts or complex chemical mixtures. This proposal is likely to be based on the broad body of literature supporting the efficacy of well-characterized herbal extracts, often proprietary, which could provide evidence of intermediate indications. Moreover, if the herbal extract remains essentially the same, there is no need (nor feasible funding) to conduct redundant clinical trials for slightly varied dosage forms.

Other technical issues flagged by CMA for review include:

- Similarly to the flexibility provided by other regulators, CMA will continue to advocate for improvements in the alignment of indications and evidence, including relating to the relevance of study outcomes.
- Review of TGA assessment of clinical benefits, including consideration of the use outcomes measures that provide valuable information on the impact of an intervention from the patient's perspective.
- Inclusion of additional statistical methods which can be applied in certain circumstances with a justification.

Background: AUST L(A) and CMA advocacy

In response to recommendations arising from the Review of Medicines and Medical Devices Regulation (MMDR), the AUST L(A) pathway for complementary medicines was introduced in 2018. The pathway, which sits between the listed (lower risk) and registered (higher risk) pathways, allows for the efficacy assessment of listed complementary medicines with higher-level indications than those in the Permitted Indications Determination with the intention of increasing availability of information to support consumer decisions. Medicines listed through the AUST L(A) pathway are included in the ARTG following self-certification of the safety and quality of the product, and TGA pre-market assessment of efficacy evidence supporting the proposed indications.

Since the introduction of the pathway, three AUST L(A) medicines have been included in the ARTG. CMA have received feedback from numerous stakeholders, including both successful and unsuccessful applicants, that excessive barriers exist in relation to the AUST L(A) evidence requirements and successful use of the pathway has been hampered as result. In response to members concerns, CMA initiated an internal review of the AUST L(A) evidence guidelines to address and resolve these identified barriers.

CMA worked throughout 2023 to promote the development of fit for purpose, risk commensurate requirements to incentivise industry AUST L(A) applications. Through our ongoing engagement with the TGA on the review of the AUST L(A) evidence guidelines and in collaboration with CMA's Scientific Advisory Working Group members, CMA advocated for ways to increase the successful use of the AUST L(A) pathway, in recognition that the full potential of the pathway has not be realised for our sector. As part of this review, CMA also sought broader member feedback and insight on proposals to improve the AUST L(A) pathway in May 2023.

June 2023 – CMA met with the TGA COMB executive staff and provided a written response to the TGA on improving implementation of the AUST L(A) pathway which outlined high level aspects of the pathway that industry identified as not operating optimally and as intended and which require review and/or adjustment.

September 2023 – CMA provided additional detailed feedback to the TGA which related to technical details of the AUST L(A) guidelines, including commentary on aspects of acceptable clinical trial data and methods of establishing efficacy.

November 2023 – CMA submitted further technical feedback to the TGA, identifying areas which may require broader review to align with generally accepted scientific methods and approaches, and proposing amendments to reduce duplication and increase clarity, increase market share, and ensure the ongoing growth of our leading academic sector.

Resources

- TGA website: Assessed listed medicine evidence guidelines
- Assessed listed medicine evidence guidelines V1.2 [PDF]
- Link to online comparison of 2018 (V1.1) and 2024 (V1.2) AUST L(A) evidence guidelines