Australian Government
Department of Health
Therapeutic Goods Administration

Mandatory requirements for an assessed listed medicine application to pass preliminary assessment

Applicable for applications lodged from March 2018

Version 1.0, March 2018

TGA Health Safety Regulation

Contents

Overview

This document describes the information (and the form of that information) that must be submitted to the TGA in order for an application to list an assessed listed medicine in the Australian Register of Therapeutic Goods (ARTG) to pass preliminary assessment and proceed to evaluation.

Scope

These requirements apply to applications to list an assessed listed medicines in the ARTG that are lodged with the TGA from March 2018, including applications to change an assessed listed medicine that results in a separate and distinct good under subsection 16(1) of the *Therapeutic Goods Act 1989* (the Act) to which the Therapeutic Goods (Groups) Order No. 1 of 2001 applies.

Background

Application for new assessed listed medicines

Applications for new listings in the ARTG as an assessed listed medicine are made under section 23B of the Act. Section 23B requires that applications:

- are made in accordance with a form or in a manner approved by the Secretary (subparagraph 23B(2)(a)(i) of the Act); and
- include such information in a form approved by the Secretary as will allow the determination of the application (subsection 23B(9) and 23B(10) of the Act)

Section 23 instruments

The Section 23 instruments specify how applications to list a complementary medicine under section 26AE of the Act ('assessed listed medicines') must be made and require applications to include the information described in the following regulatory documents in order to pass preliminary assessment and proceed to evaluation:

- Mandatory requirements for an effective assessed listed medicine application (this document); and
- CTD Module 1: Administrative information for assessed listed medicines

Mandatory requirements

Organisation and format of the application dossier

The applicant must provide an application dossier that has been completed and structured in accordance with the relevant instructions specified in:

- CTD Module 1: Administrative information for assessed listed medicines: completed to the extent that it is applicable for all assessed listed medicines application levels.
- Module 2: Overviews, written summaries and tabulated summaries of the data contained in Module 5, completed to the extent that it is applicable for particular L(A)2 and L(A)3 applications as detailed in Appendix A: Specific technical data requirements (Module 2).
- Module 5: ICH M4E Common technical document for the registration of pharmaceuticals for human use - Efficacy (CPMP/ICH/2887/99 Rev 1 Efficacy). Completed to the extent that it is applicable for particular L(A)2 and L(A)3 applications, as detailed in Appendix A: Specific technical data requirements.

The application dossier must be submitted electronically, in accordance with the requirements in the General dossier requirements.

Content of the application dossier

The application dossier must provide appropriate documentation (in the correct format and locations, as determined by the CTD modules) to allow a delegate of the Secretary to decide whether the medicine can be approved for listing in the ARTG. The exact content of the application dossier will vary according to the application level and type of medicine.

Technical data requirements

The technical information that is required in Module 5 for an application to be considered effective is at Appendix A – Specific technical data requirements.

Where an application meets the description of more than one of the application types listed in Appendix A - Specific technical data requirements, data must be provided in accordance with the requirements for each application type that is relevant to the application.

Comparable overseas regulator (COR) reports

The TGA makes use of reports from comparable overseas regulators (CORs), where possible, in the regulation of registered complementary medicines, new ingredients for use in listed medicines and most recently in evaluation of assessed listed medicine applications.

Introducing a framework that accepts COR reports allows us to complete evaluations within shorter timeframes. The framework allows technical data from identified regulators to be used and adapted to meet Australian requirements, provided the regulator meets the criteria of a suitable COR.

Where COR reports are used, we will continue to make the final regulatory decision, ensuring efficacy data is not compromised and that the Australian regulatory context is taken into account.

The criteria for identifying CORs and submission requirements are currently being finalised by the TGA and will be published in due course.

Australia-specific and adopted European Union and ICH guidelines

It is the applicant's responsibility to identify and familiarise themselves with the relevant Australia-specific guidelines and adopted European Union (EU) and ICH guidelines.

The use of European Union (EU) and ICH guidelines adopted in Australia and other Australia-specific guidelines is not mandated in the legislation. However, under paragraph 25(1)(d) of the Act the delegate is required, when evaluating an application for registration, to consider:

> *"…whether the quality, safety, and efficacy of the goods for the purposes for which [the goods] are to be used have been satisfactorily established."*

Australia-specific guidelines and adopted EU and ICH guidelines describe the kind of data and information to be included in each Module of a dossier. If the dossier does not contain all information required for pre-market assessment for efficacy, the TGA may not be able to determine whether the efficacy of the medicine has been satisfactorily established.

Please note

The TGA has an ongoing process to consider and decide whether or not to adopt newly released and updated EU and ICH guidelines. As part of this process, some of the above guidelines may be amended, removed or replaced from time to time. Applicants should check the TGA website routinely and subscribe to the email list to receive updates on new content.

Justification for not complying with technical data requirements or not adhering to guidelines

Compliance with relevant requirements set out in Appendix A – Specific technical data requirements and adherence to applicable guidelines is highly desirable as it most readily allows the TGA to determine whether the medicine can be listed in the ARTG.

Where there are any deviations from relevant requirements or applicable guidelines, the applicant must advise the TGA and provide a justification.

When a justification needs to be provided

If the application does not meet a technical requirement or adhere to an applicable guideline, a justification must be provided.

For instance, a justification must be provided when:

- the dossier does not contain a Module that is required for the application to be considered effective and accepted for evaluation.
- the application does not adhere, either in full or in part, to the guidelines that set out the required technical information.

What needs to be included in a justification

Where the TGA has provided detailed information to assist applicants to construct a justification, ensure **all** details have been addressed in the justification. For example, the TGA Biopharmaceutic studies guideline provides information on the required content for a justification for not conducting biopharmaceutic studies.

In other cases, applicants need to make a separate robust scientific justification for each deviation from relevant data requirements or applicable guidelines. The justification must include all of the following for the application to be effective:

- an explanation of the requirement, guideline or part of the guideline that is not being met, and how it is not being met
- citations of relevant scientific studies supporting the reasons why the guideline or requirement cannot be met
- an explanation of the proposed alternative approach and a contemporary scientific justification for why the approach is valid, with reference to supporting documents
- validation of the alternative approach, including reference to supporting documents, including TGA documents, where appropriate
- citations of relevant scientific studies supporting the alternative approach
- literature based submissions must be in accordance with TGA guidance on Literature based submissions and the Assessed listed medicines evidence guidelines.
- full text versions of all cited references (other than TGA documents) in the dossier.

Purpose of justifications

Each justification performs two functions:

- It needs to be present and address all of the above points for each relevant requirement that is not met or applicable guideline that is not adhered to, in order for the application to be considered effective under section 23B of the Act and be accepted by the TGA for evaluation; and
- Once the application has been accepted for evaluation, each justification needs to be sufficient for the TGA to be satisfied that the medicine can be listed in the ARTG under section 26AE of the Act. The content and merit of a justification (i.e. whether the alternative approach is in fact valid) will be assessed during the evaluation phase.

Justifications that are not complete and/or scientifically sound will not be accepted. This may result in an application for listing of a medicine being rejected.

Compliance with administrative requirements

Applicants must comply with, and cannot provide a justification for not complying with, administrative requirements as set out in:

- this document; Organisation and format of the application dossier
- CTD Module 1: Administrative information for assessed listed medicines
- General dossier requirements
- the approved application form in TGA Business Services.

Appendix A – Specific technical data requirements

Where an application meets the description of more than one of the application types listed in this appendix, data must be provided in accordance with the requirements for each application type that is relevant to the application. Where these tables refer to the data requirements described in European Union (EU) guidelines that have been adopted by the TGA, the guidance should be read in conjunction with any applicable TGA annotation.

Requirements for L(A)1 applications

- CTD Module 1: Administrative information for assessed listed medicines including:
  - Co-marketed medicines declarations (letters of authorisation) (section 1.5.5).
  - Assessed listed medicine assurances (section 1.5.7).

Requirements for L(A)2 applications

- CTD Module 1: Administrative information for assessed listed medicines including:
  - For applications using the Comparable overseas regulator (COR) report based process, provide the assessment and other information as described in the document 'Comparable overseas regulators (CORs) for complementary medicines – guidance for use of COR reports in Module 1' (section 1.11).
  - For generic based applications, provide Summary of bioavailability or bioequivalence study (section 1.9.1) or Justification for not providing biopharmaceutic studies (section 1.9.2).
- Module 2 (only for generic based applications)
- Module 5 (only for applications providing biopharmaceutic data).

Requirements for L(A)3 applications

- CTD Module 1: Administrative information for assessed listed medicines
- Module 2
- Module 5

Table 1: Module 2 CTD Summary

Only part of CTD Module 2 is required to be submitted for assessed listed medicines to provide a place for sponsors to provide overviews and ensure they are in the correct format.

Application type	CTD module	Module 2 requirement
L(A)2 Generic based application	2.5	Provide Module 2.5 completed in accordance with ICH M4E Common technical document for the registration of pharmaceuticals for human use - Efficacy (CPMP/ICH/2887/99 Rev 1 Efficacy) to the extent that it is applicable. For example, for a generic medicine application where Module 5 only consists of a bioequivalence study (Module 5.3.1), Module 2.5 would consist of a clinical overview of the findings (section 2.5.2) from the bioequivalence study together with any other relevant information.
L(A)3	2.5	Provide Module 2.5 completed in accordance with ICH M4E Common technical document for the registration of pharmaceuticals for human use - Efficacy (CPMP/ICH/2887/99 Rev 1 Efficacy) to the extent that it is applicable. For example, where multiple clinical studies are provided, this section should provide a critical analysis of the data with the purpose of demonstrating efficacy for the relevant indication(s) (section 2.5.4) together with any other relevant information. The overview should provide a logical summary of how all the evidence comes together to support the indication(s).

Table 2: Module 5 – Efficacy evidence: General application requirements

The table below refers to the corresponding CTD Module for providing efficacy evidence to support L(A)2 and L(A)3 applications. Complete the Module 5 requirements in accordance with ICH M4E Common technical document for the registration of pharmaceuticals for human use - Efficacy (CPMP/ICH/2887/99 Rev 1 Efficacy) to the extent that it is applicable. The Assessed listed medicines evidence guidelines outlines different methods for establishing efficacy (refer to section 4. 'Evidence requirements and standards' and section 5. 'Alignment of indications and evidence').

Application type (more than one type may apply)	CTD Module	Module 5 Requirement
Applications that include biopharmaceutic or pharmacokinetic data	5.3.1	Provide study reports in accordance with requirements detailed in: · Assessed listed medicines evidence guidelines · Guidance 15: Biopharmaceutic Studies Note: if an Australian originator reference medicine used, it must have been registered on the basis of a full dossier.
Applications that include clinical study reports	5	Provide study reports in accordance with requirements detailed in: · Assessed listed medicines evidence guidelines · Any other specific Australian or EU guidelines relevant to the medicine.
Applications that are fully or partly literature based (literature based submission)	5.4	Provide copies of the reference documents in accordance with the TGA guidance: · Assessed listed medicines evidence guidelines · Literature-based submissions for complementary medicines.

Table 3. Module 5 – Efficacy evidence: L(A)2 requirements (generic based applications)

The table below refers to the corresponding CTD Module for providing efficacy evidence to support generic based L(A)2 applications. Complete the Module 5 requirements in accordance with ICH M4E Common technical document for the registration of pharmaceuticals for human use - Efficacy (CPMP/ICH/2887/99 Rev 1 Efficacy) to the extent that it is applicable.

Application type (more than one type may apply)	CTD Module	Module 5 requirement
Generic medicines (oral immediate release), other than those specifically excluded from requiring biopharmaceutic data in Guidance 15: Biopharmaceutic - Studies Medicines that do not require biopharmaceutic data	5.3.1	Provide biopharmaceutic study reports in accordance with the requirements for generic medicines detailed in: · Assessed listed medicines evidence guidelines · Guidance 15: Biopharmaceutic Studies
Generic modified release oral medicine	5.3.1	Provide the biopharmaceuitic study reports in accordance with the requirements detailed in: · Assessed listed medicines evidence guidelines · Guidance 15: Biopharmaceutic Studies · Guidance on the pharmacokinetic and clinical evaluation of modified release dosage forms (EMA/CPMP/EWP/280/96 Corr1). (Efficacy component only).
Any other generic medicines	5.3.1	Provide biopharmaceutic study reports in accordance with the requirements for generic medicines detailed in: · Assessed listed medicines evidence guidelines · Guidance 15: Biopharmaceutic Studies Note: If clinical efficacy is required to demonstrate therapeutic equivalence, then this is not suitable for the L(A)2 pathway (e.g. generic topical medicine).

Table 4. Module 5 – Efficacy evidence: L(A)3 applications

The table below refers to the corresponding CTD Module for providing efficacy evidence for L(A)3 applications. Complete the Module 5 requirements in accordance with ICH M4E Common technical document for the registration of pharmaceuticals for human use - Efficacy (CPMP/ICH/2887/99 Rev 1 Efficacy) to the extent that it is applicable.

Application type (more than one type may apply)	CTD Module	Module 5 requirement
New strength	5	Provide data in accordance with: · Assessed listed medicines evidence guidelines · For medicines that are systemically absorbed (e.g. oral tablets), provide comparative bioavailability/bioequivalence study reports in accordance with Guidance 15: Biopharmaceutic Studies · For locally applied, locally acting medicines, provide data in accordance with the EU document Clinical requirements for locally applied, locally acting products containing known constituents. (Efficacy component only) · Any other specific Australian or EU guidelines relevant to the medicine.
New dosage form	5	Provide data in accordance with: · Assessed listed medicines evidence guidelines · For systemically absorbed dosage forms provide study reports in accordance with Guidance 15: Biopharmaceutic Studies · Any other specific Australian or EU guidelines relevant to the medicine.

Application type (more than one type may apply)	CTD Module	Module 5 requirement
New modified release dosage form	5	Provide data in accordance with: · Assessed listed medicines evidence guidelines · Any other specific Australian or European Union (EU) guidelines relevant to the medicine, including the Guidance on the pharmacokinetic and clinical evaluation of modified release dosage forms (EMA/CPMP/EWP/280/96 Corr1). (Efficacy component only). · Any other specific Australian or EU guidelines relevant to the medicine.
New route of administration	5	Provide data in accordance with: · Assessed listed medicines evidence guidelines · Any other specific Australian or EU guidelines relevant to the medicine.
New indications or directions for use (including different dose, method of administration, frequency or duration and target population)	5	Provide data in accordance with: · Assessed listed medicines evidence guidelines · Any other specific Australian or EU guidelines relevant to the medicine.
New fixed combination medicine or composite packs containing multiple active ingredients	5	Provide data in accordance with: · Assessed listed medicines evidence guidelines · Complementary medicines presented as composite packs or kits · Any other specific Australian or European Union (EU) guidelines relevant to the medicine, including the Guideline on Clinical Development of Fixed Combination Medicinal Products (CPMP/EWP/240/95 Rev1), adopted by the TGA. (Efficacy component only).

Application type (more than one type may apply)	CTD Module	Module 5 requirement
Locally applied, locally acting medicine (e.g. topical medicine)	5	Provide data in accordance with: · Assessed listed medicines evidence guidelines · Any other specific Australian or European Union (EU) guidelines relevant to the medicine, including the guideline Clinical requirements for locally applied, locally acting products containing known constituents. (Efficacy component only).
Any other new product	5	Provide data in accordance with: · Assessed listed medicines evidence guidelines · Any other specific Australian or EU guidelines relevant to the medicine.

Version history

Version	Description of change	Author	Effective date
V1.0	Original publication	Complementary and OTC Medicines Branch, TGA	March 2018

Therapeutic Goods Administration

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