Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

Mandatory requirements for an effective application to vary the Permissible Ingredients Determination

For applications lodged from February 2023

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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 under section 26BD of the Therapeutic Goods Act ('the Act') to vary the Therapeutic Goods (Permissible Ingredients) Determination (the 'Permissible Ingredients Determination') to pass preliminary assessment and proceed to evaluation.

Scope

These requirements apply to applications for the addition of new ingredients, or variation of existing ingredients, as listed in the Permissible Ingredients Determination, that are lodged with the TGA from 1 February 2023, including applications for a proposed new role, route of administration, or a change to the existing requirements for use of a current permitted ingredient.

Background

Application to vary the Permissible Ingredients Determination

All listed medicines (AUST L listed medicines and AUST L[A] assessed listed medicines) may only contain ingredients included in the Permissible Ingredients Determination. The Permissible Ingredients Determination is a legislative instrument made by the Minister for Health under section 26BB of the Act.

For a new substance to be included or an existing substance to be varied in the Permissible Ingredients Determination, an applicant must make an application to the Secretary under section 26BD of the Act for a recommendation that the Minister vary the Permissible Ingredients Determination.

Subsection 26BD(3) requires that applications:

- are made in accordance with a form determined by the Secretary; and
- be accompanied by the kind of information determined by the Secretary.

Therapeutic Goods (Permissible Ingredients—Information that Must Accompany Application for Variation) Determination 2023

The *Therapeutic Goods (Permissible Ingredients—Information that Must Accompany Application for Variation) Determination 2023* specifies how applications for substances to vary the Permissible Ingredients Determination must be made and requires applications to include the information described in the 'Mandatory requirements for an application to vary the Permissible Ingredients Determination' (this document) in order to pass preliminary assessment and proceed to evaluation.

Substance applications

For information on the different levels of substance applications (IN1-IN4) that are referred to in this document, the application process, and further detail on individual requirements, please see:

- Application requirements for new substances in listed medicines – Australian regulatory guidelines
- Evaluation of substances for use in listed medicines: application user guide
- Comparable Overseas Bodies (COBs) for complementary medicines

Mandatory requirements

Organisation and format of the application dossier

The dossier must contain folders that are named and structured corresponding to the core information requirements that are relevant to the application category as specified in Appendix A: Specific mandatory 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 information as specified in Appendix A: Specific mandatory requirements.

Comparable overseas bodies (COB) reports

For the criteria to identify COBs, the current list of COBs and the process for using COB reports, refer to Comparable Overseas Bodies (COBs) for complementary medicines.

An evaluation using reports from a COB involves an assessment of the application against the Australian mandatory requirements. These evaluations are performed under abridged timeframes. As such, you must provide:

- A completed COB report-based process - Substance evaluation checklist for each COB report provided;
- A full un-redacted English copy of the COB evaluation report(s); and
- Information in accordance with the application category as specified in Appendix A: Specific mandatory requirements.

If there is a significant amount of data that requires evaluation beyond the COB report, it may be determined that the application must be evaluated under a different application category rather than the abridged COB category.

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 EU and ICH guidelines adopted in Australia and other Australia-specific guidelines is not mandated in the legislation. However, under subsection 26BE(5) of the Act the delegate is required, when deciding whether to make a recommendation, to have regard to:

"(a) the quality and safety of the ingredients concerned; and

(b) such other matters (if any) as the Secretary considers relevant."

Australia-specific guidelines and adopted EU and ICH guidelines describe the kind of data and information to be included in a dossier. If the dossier does not contain all information required for pre-market assessment, the TGA may not be able to determine whether the quality and safety have 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 mandatory requirements or not adhering to guidelines

Provision of data in all categories set out in Appendix A – Specific mandatory requirements and adherence to applicable guidelines is highly desirable as it most readily allows the TGA to determine whether the substance can be used in listed medicines.

When a justification needs to be provided

If the application does not meet a technical requirement defined in Appendix A, or adhere to a guideline that is relevant to the substance, a justification must be provided. The tables in Appendix A state which core information requirements a justification will not be accepted for.

Further guidance on providing justifications can be found in the Application requirements for new substances in listed medicines – Australian regulatory guidelines.

The content and merit of a justification (i.e. whether the alternative approach is appropriate) will not be assessed during the preliminary assessment phase but during the evaluation phase.

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

- Organisation and format of the application dossier
- General dossier requirements
- the approved application form in TGA Business Services.

Appendix A – Specific mandatory requirements

Requirements for IN1 applications

- Administrative requirements as specified in Table 1.
- Evaluation of safety and quality based on evaluation report(s) from a COB:
  - Provide the information specified in Comparable overseas bodies (COB) reports above.
  - Provide a gap analysis:
    - discussing how the information satisfies each core information requirement in Table 3 and Table 4; and
    - to determine any relevant data that may have been generated since the COB report was approved (e.g. an updated literature search or new adverse event reports).
  - Provide a compositional guideline for substances not subject to a monograph in a default standard.
- Evaluation of safety based on evaluation report(s) from a COB and evaluation of quality based on a monograph contained in a default standard:
  - Provide the information specified in Comparable overseas bodies (COB) reports above.
  - Provide a gap analysis:
    - discussing how the information satisfies each core information requirement in Table 4; and
    - to determine any relevant data that may have been generated since the COB report was approved (e.g. an updated literature search or new adverse event reports).
  - Provide supporting data for the core information requirements in Table 2.

Requirements for IN2 applications

- Administrative requirements as specified in Table 1.
- Evaluation of safety based on evaluation report(s) from a COB:
  - Provide the information specified in Comparable overseas bodies (COB) reports above
  - Provide a gap analysis:
    - discussing how the information satisfies each core information requirement in Table 4; and
    - to determine any relevant data that may have been generated since the COB report was approved (e.g. an updated literature search or new adverse event reports).
- Independent evaluation of quality by the TGA:

- Provide supporting data for each core information requirement in Table 3.

Requirements for IN3 applications

- Administrative requirements as specified in Table 1.
- Independent evaluation of safety by the TGA:
  - Provide supporting data for each core information requirement in Table 4.
- Evaluation of quality based on evaluation report(s) from a COB:
  - Provide the information specified in Comparable overseas bodies (COB) reports above
  - Provide a gap analysis:
    - discussing how the information satisfies each core information requirement in Table 3; and
    - to determine any relevant data that may have been generated since the COB report was approved.
  - Provide a compositional guideline for substances not subject to a monograph in a default standard.
- Evaluation of quality based on a monograph contained in a default standard:
  - Provide supporting data for the core information requirements in Table 2.

Requirements for IN4 applications

- Administrative requirements as specified in Table 1.
- Full independent evaluation of safety and quality by the TGA:
  - Provide supporting data for each core information requirement in Table 3 and Table 4.

Table 1 - Administrative information required for all applications

Provide the information in accordance with 'SECTION B – Information requirements' in Application requirements for new substances in listed medicines – Australian regulatory guidelines.

Core information requirement	
Covering letter/overview of the application *No justification will be accepted for the absence of this requirement*	The cover letter must: • be on a company letterhead • be signed by a person authorised to conduct business on behalf of the applicant. The person must be listed on the TGA client database and may be a company employee or an agent. The 'AU eCTD specification: Module 1 and regional information contains information about electronic signatures • include: – the purpose of the application – details of correspondence with us if you have submitted a proposal for a new name, where the substance did not have an existing TGA approved name – the contact person and sponsor name – the rationale for selecting the application category. Include information that is significant for determining the application category and technical information requirements – other relevant background information, such as overseas regulatory status. • notify us if you are providing a detailed justification for not complying with technical information requirements and/or not adhering to applicable guidelines, and the location of each justification in your dossier.

Core information requirement	
Table of contents *No justification will be accepted for the absence of this requirement*	A comprehensive table of contents (a complete list of all documents in the dossier), with location references for each document. The table of contents can be provided for the complete dossier or for administrative, quality and safety data separately. Provide hyperlinks to each section.
Record of any pre-submission meeting or correspondence	Include information in this section if you had a pre-submission meeting or correspondence with us in relation to your application. For pre-submission meetings, include a copy of the pre-submission meeting record. For pre-submission correspondence via email, include a copy of the relevant email correspondence.
Request for confidentiality (if desired)	You may request that data contained in your application remain commercially confidential—see Treatment of information provided to the TGA. Where required, identify data that is not in the public domain and may be commercially confidential.

Table 2 - Information required to demonstrate QUALITY for substances subject to a monograph in a default standard

Provide the information in accordance with 'SECTION B – Information requirements' in Application requirements for new substances in listed medicines – Australian regulatory guidelines.

Core information requirement	
Specification control *No justification will be accepted for the absence of this requirement*	• For a substance that is subject to a monograph in a default standard (BP, Ph. Eur or USP), provide a full un-redacted English copy, or name and version number of the current monograph. • For a substance that is intended for use as an active ingredient, provide a certificate of analysis for minimum one commercial scale batch (or two pilot scale batches) to demonstrate full compliance with the monograph specifications. • For a substance only intended for use as an excipient ingredient, provide an assurance that the substance meets the monograph specifications.

Table 3 - Information required to demonstrate QUALITY for substances not subject to a monograph in a default standard

Provide the information in accordance with 'SECTION B – Information requirements' in Application requirements for new substances in listed medicines – Australian regulatory guidelines.

Core information requirement	
Description *No justification will be accepted for the absence of this requirement*	Description of the substance. State if the substance is derived from or contains genetically modified substances. • If the substance is derived from a genetically modified organism, or genetically modified organism is used during manufacture, demonstrate absence of this in final substance. • If the substance is a live microorganism that has been genetically-modified, provide a declaration that the organism is exempt under Schedule 2 of the Gene Technology Regulations 2001.

Core information requirement		
Manufacturing details		Description of manufacturing process, control of materials, critical steps & intermediates, process development, process validation. For chemically derived excipients for dermal use only, provide a brief description of manufacturing process.
Characterisation	**General properties**	A list of physico-chemical properties of the substance and acceptance criteria. For live microorganisms, provide additional information to address antimicrobial resistance and susceptibility, absence of virulence factors, toxigenic and pathogenic attributes of the strain under evaluation.
	Identity	Identification test(s) specific for the substance using pharmacopeial or validated methods, and acceptance criteria that can unambiguously distinguish the substance from any other substance or closely related polymorphic forms.
	Assay	Test(s) using pharmacopeial or validated methods, and acceptance criteria that determine the presence and quantity (content) of a specific substance. For herbal materials, this may be based on marker compounds. For excipients for dermal use only, an assay test is not a requirement when only used in a formulation for their physical properties (e.g. emulsifier, thickener).
	Impurities and incidental constituents	A list of impurities and incidental constituents that may be present in the substance, using pharmacopeial or validated methods, and acceptance criteria that determine the presence and quantity of the impurity.
	Reference standard	Information about the reference standards for use as the standard in tests, such as identity, assay and impurities testing. For chemically derived excipients for dermal use only, a reference standard is not required.

Core information requirement	
Specifications	A compositional guideline, comprising of a list of tests, reference to validated analytical procedures and appropriate acceptance criteria using the compositional guideline template. For substances intended for use as an active ingredient, provide certificates of analysis for minimum two commercial-scale batches or three pilot-scale batches, to demonstrate compliance with the proposed compositional guideline. For substances for excipient use only, provide a certificate of analysis for at least one commercial-scale batch or two pilot-scale batches to demonstrate compliance with the proposed compositional guideline.
Stability test	Real-time and accelerated stability testing data for two commercial scale batches or three pilot scale batches. Stability testing is not required if stress testing data can be provided that demonstrates the absence of degradants. For excipients for dermal use only, no stability or stress testing data is required.

Table 4 - Information required to demonstrate SAFETY

Provide the information in accordance with 'SECTION B – Information requirements' in Application requirements for new substances in listed medicines – Australian regulatory guidelines.

Core information requirement (required for each route of administration proposed)		
Systematic literature search		A systematic literature search on the substance; with the search strategy and results with justification for inclusion/exclusion of data.
History and pattern of human use		Information on: • Use in therapeutic goods (Australian and International) • Use in food • Traditional use • History of safe use • Summary of overall human exposure from all sources.
Biological activity	**Pharmacokinetics**	Pharmacokinetic studies addressing: • Absorption • Tissue distribution and storage • Metabolism • Mode and extent of excretion or elimination. For substances for dermal use on unbroken skin only, that are demonstrated to not be absorbed beyond the *stratum corneum*, no other pharmacokinetic information is required. For microorganisms, only information to demonstrate its absence in the systemic circulation of the host is required.

Core information requirement (required for each route of administration proposed)		
	Pharmacodynamics	For substances that are systemically absorbed, or where systemic absorption cannot be excluded, pharmacology information addressing: • Primary pharmacodynamics • Safety pharmacology to study the effects of the substance on the following vital functions: – Central nervous system – Cardiovascular system – Respiratory system • Known pharmacodynamic drug interactions For substances for dermal use on unbroken skin only, that are demonstrated to not be absorbed beyond the *stratum corneum* and do not react with the skin, pharmacodynamics information is not required. For microorganisms, only information addressing the following are required: • Mechanisms of action • Known interactions with: – Antibiotics/antifungals (only applicable to live microorganisms) – Host immunity

Core information requirement (required for each route of administration proposed)	
Toxicological data	Information from *in vitro* studies, animal studies, human clinical studies or other information (or a combination) addressing: • Maximum daily dosage • Duration of use • Genotoxicity • Carcinogenicity (if continuous use of at least 6 months intended) • Reproductive and developmental toxicity (if there are no restrictions proposed in the application that limit use of the substance for use in pregnant or lactating females, or in a paediatric population <18 years) • Local tolerance For substances for dermal use on unbroken skin only, that are demonstrated to not be absorbed beyond the *stratum corneum* and do not react with the skin, only information to address the following is required: • Local tolerance • *In silico* analysis for mutagenicity if potential exposure to other tissues (e.g. oral exposure if substance applied on face). For microorganisms, information addressing genotoxicity is not required.
Adverse reactions	A list of the nature, severity and frequency of adverse reactions from adverse event databases, clinical trials, or case reports of human poisoning.
Substances of human or animal origin	Information on clearance of risk for transmissible spongiform encephalopathy (TSE) if substances of human or animal origin were used during manufacture. For microorganisms, this information is not required.

Version history

Version	Description of change	Author	Effective date
V1.0	Original publication	Complementary and Over the Counter Medicines Branch	February 2023

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