Systematic Literature Search for Complementary and OTC Medicine applications

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Presentation overview

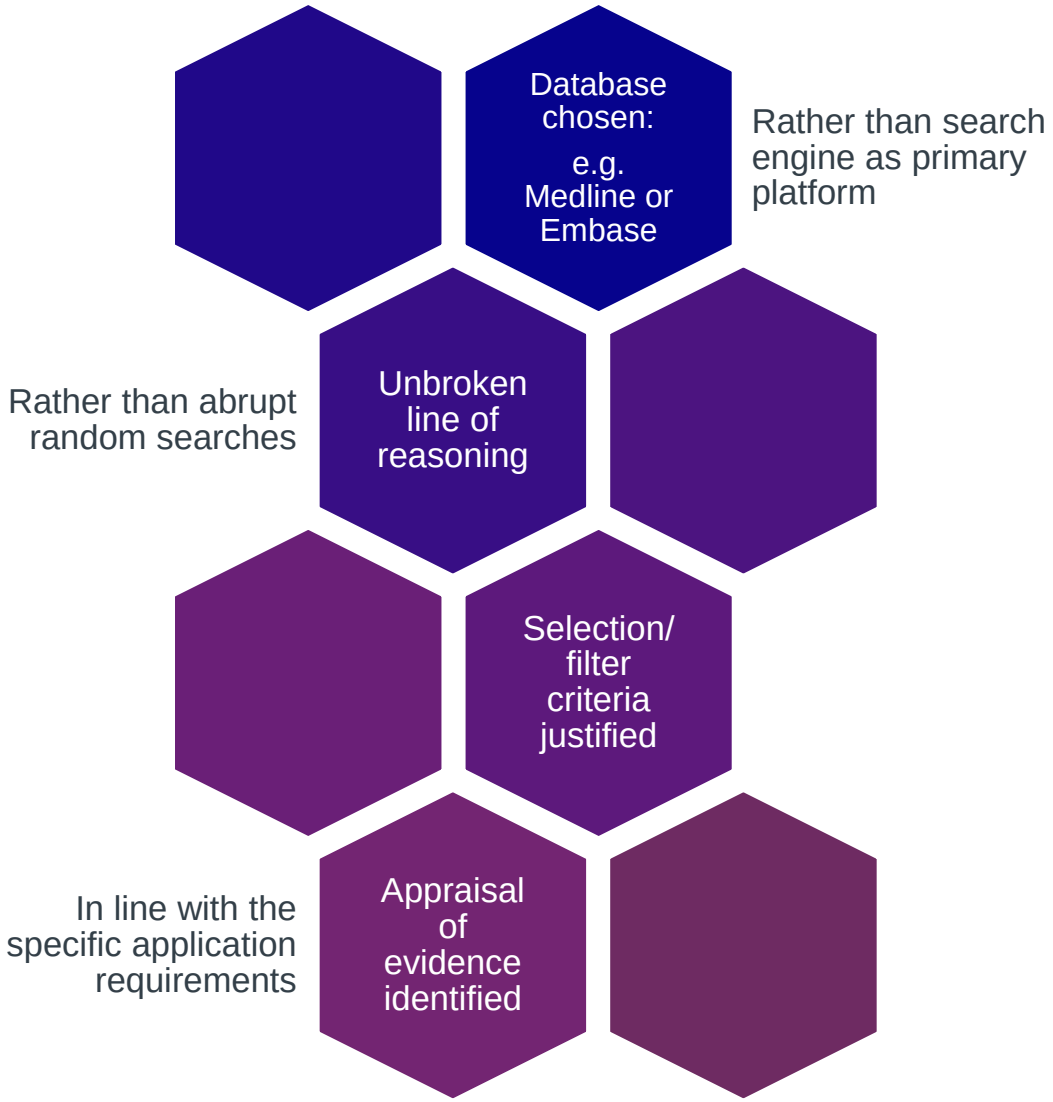
1. Introduction
2. When a Literature Based Submission (LBS) may be appropriate for non-prescription medicines
3. Application categories that may be suitable for LBS
4. Dossier requirements
5. Common issues

Systematic literature search is crucial when compiling a Literature based submission (LBS)

These submissions are relevant to applications that require data to support safety and/or efficacy claims.

This is relevant to both application to list/register and application to vary existing medicines/substances.

Key aspects of systematic literature searches



When an LBS may be appropriate for Non-prescription Medicines

Listed and Registered complementary Medicines (RCM)

• compiling an evidence package to support indications made for a listed medicine

• an application for the evaluation of a substance for use as a new ingredient in listed medicines

• an application for evaluation of a new assessed listed (L(A)) medicine

• an application for a new RCM (less common)

• an application for changes to the indications or label claims or directions for use for L(A) medicines

• an application for changes to RCM, including changes to:

– indications or label claims

– directions for use

– clinical or non-clinical aspects of the Product Information

Reference: Literature-based submissions for listed medicines and registered complementary medicines V1.0 May 2020

When an LBS may be appropriate for Non-prescription Medicines

OTC Medicines

If company study reports do not exist or insufficient, an LBS may be appropriate. Examples of application types include:

- changes to indications or label claims
- changes to directions for use
- changes to clinical or non-clinical aspects of the Product Information
- new medicine applications (less common)

For additional guidance on when an LBS may/may not be suitable, refer to Pre-submission guidance for literature based submissions (LBS) | Therapeutic Goods Administration (TGA)

Reference: ARGOM - OTC medicines – Safety and efficacy data – Section 4.1 Literature-based submissions

Application categories where an LBS may be suitable

Type	Category	Reference
RCM (New medicine)	RCM4 •The application has been evaluated by a COB and only required TGA evaluation of 2 of the following: safety; quality; efficacy; •A registered medicine with a change of one of the following: Increased indications, new directions or increased population RCM5 •Requires full independent evaluation by the TGA; •A registered medicine with a change to : new dosage form, new active ingredient, increased strength of active ingredient or additional excipient •Different patient population	Mandatory requirements for an effective registered medicines application V1.1 July 2021 Applications for registered complementary medicines (Formerly ARGCM V8.0 Part D) V1.0 May 2020
RCM (Change to medicine)	C3 Changes identified in the changes Table as application level C3	Changing a registered complementary medicine: RCM application levels and changes tables V1.0 May 2020
	C4 Changes identified in the changes Table as application level C4	

Application categories where an LBS may be suitable

Type	Category	Reference
New or existing substance for use in Listed Medicines	IN1 and IN2 •Evaluation of safety based on evaluation report(s) from a COB. Updated literature search is presented as part of the gap analysis. IN3 and IN4 •Full Independent evaluation of safety by the TGA.	Mandatory requirements for an application to vary the Permissible Ingredients Determination V1.0 February 2023 Guidance on using comparable overseas bodies reports V2.0 February 2023
Assessed listed medicine (New Medicine)	L(A)2 •Identical to a medicine evaluated by a COB. L(A)3 •Includes new products or variation to an existing assessed listed medicine.	Assessed listed medicines evidence guidelines V1.1 August 2018 Guidance on using comparable overseas bodies reports V2.0 February 2023
Assessed listed medicine (Change to medicine)	L(A)C2 •Changes identified in the Change Tables with the application level as C2.	Changing a listed or assessed listed medicines: application levels and change tables V2.2 March 2022

Application categories where an LBS may be suitable

OTC Medicines

- OTC applications that may require supporting safety and/or efficacy data include those submitted at the N4, N5, C3 and C4 application levels
- Where supporting safety and/or efficacy data are required, need to consider whether an LBS is capable of meeting the needs either in full or in part (i.e. along with clinical studies etc)
- Need to refer to relevant guidelines for assistance in making such a decision
- Unlikely that an LBS (alone) would be capable of meeting the data requirements for a ‘new’ (non-generic) medicine registration application

Application categories where an LBS may be suitable

Type	Category	Reference
OTC (New medicine)	N4 An application for a 'generic' medicine that: requires supporting safety and/or efficacy (clinical/toxicological) data or a justification for not providing the data.	ARGOM - OTC application categorisation framework (Version 1.2 June 2017)
OTC (New medicine)	N5 An application for a new medicine that is an extension to a 'Generic category' medicine including: •New therapeutic indications •New strength •New dosage form •New directions •New combination medicines •Different patient population **OR** An application for a medicine containing a new chemical entity as an active ingredient.	

Application categories where an LBS may be suitable

Type	Category	Reference
OTC (Change to medicine)	C3 Changes identified in the Changes Table as application level C3	Changing an OTC medicine: using the Changes Tables | Therapeutic Goods Administration (TGA)
	C4 Changes identified in the Changes Table as application level C4	

Dossier requirements for OTC, RCM, L(A)

- Formatted in line with CTD modules by means of:
  - Organising the dossier
  - Folders containing references

CTD module 1.5.1 Literature-based submission documents

This section applies to applications that partially or completely rely on literature-based data.

Follow the guidance on Literature-based submissions for listed medicines and registered complementary medicines.

Prepare and include the following in Module 1.5.1:

- methodology of the literature search, including complete details of database search strategies
- the complete search output

Include the overview summary reports in Module 2.5.

Nonclinical overview (CTD Module 2.4)

Provide an integrated and critical assessment of the pharmacological, pharmacokinetic and toxicological data for the medicine.

Clinical overview including risk benefit analysis of the medicine (CTD Module 2.5)

Provide a critical scientific analysis of the clinical data.

CTD module 4 Nonclinical data for a new registered complementary medicine ____ 22

Pharmacology ____ 23

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Secondary pharmacodynamics: *in vitro* and *in vivo* ---- 23

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Controlled and uncontrolled efficacy clinical trials ---- 26

Efficacy-related PI/CMI comments (where applicable) ---- 26

Data requirements for generic registered complementary medicines ---- 26

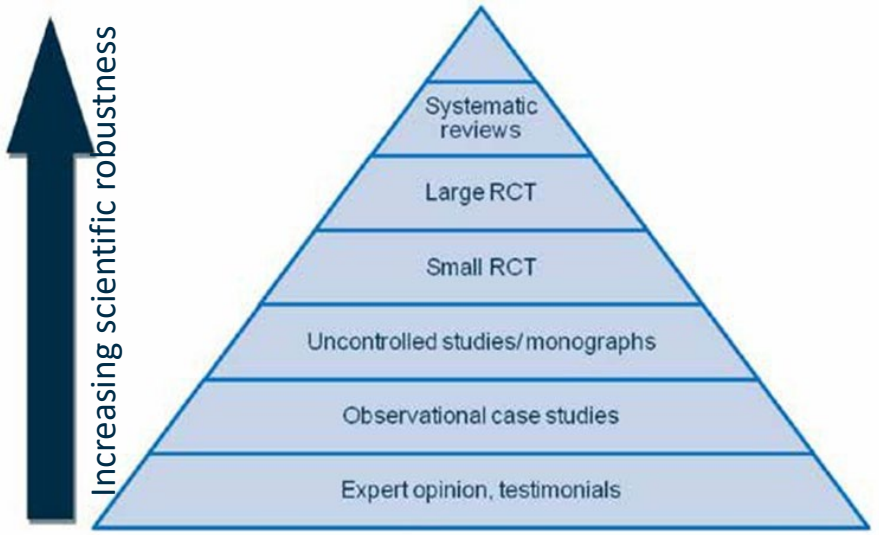
Dossier requirement for Substance applications

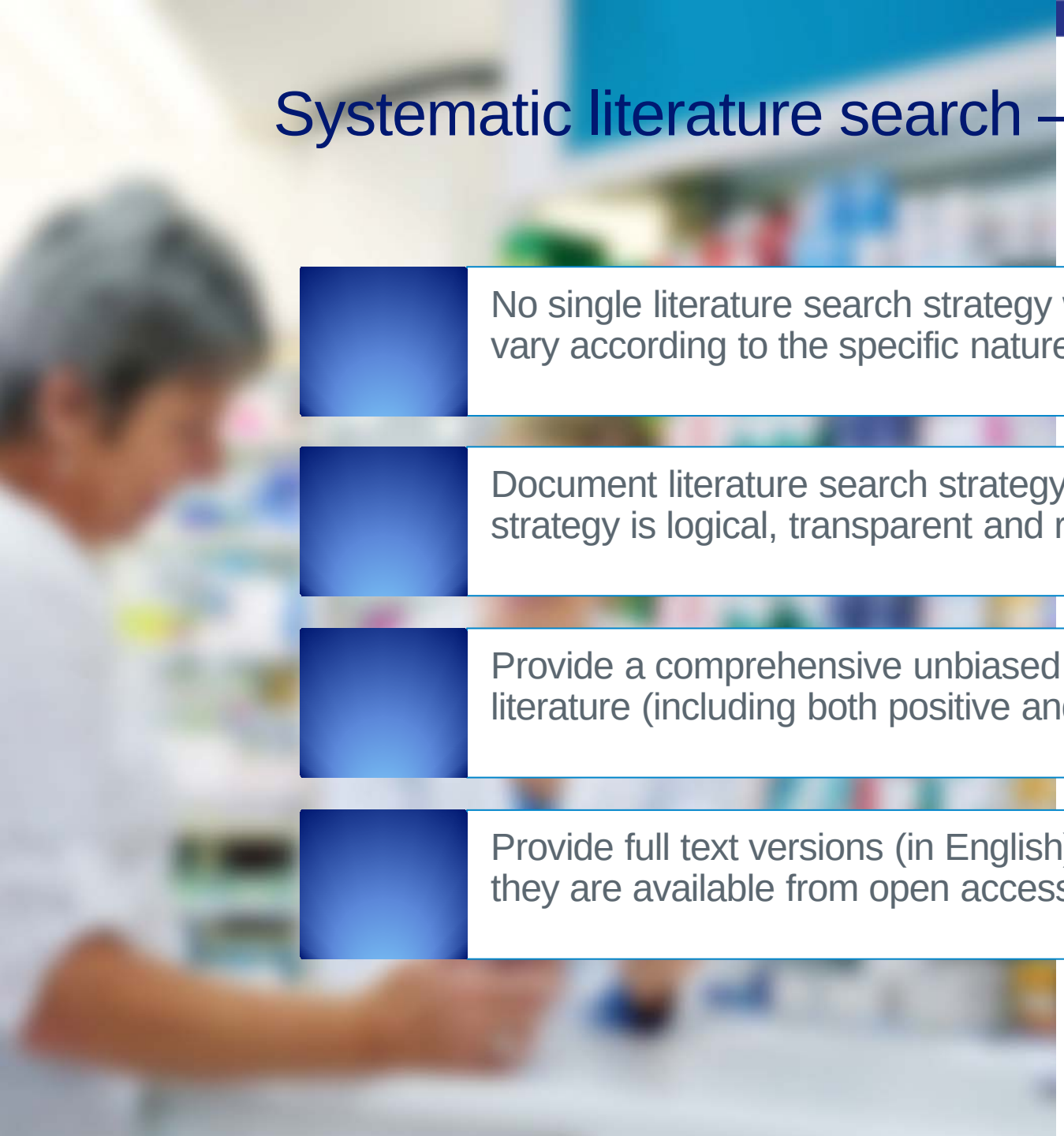
- See Table 3 (in Appendix) in ARNS for a summary of requirements for different ingredients.

Core information requirement			Substances for oral use[3]	Micro-organisms[4]	Dermal active substances[5]	Dermal excipient substances[5]
SAFETY						
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	✓	△[11]	✓	✓
		• Tissue distribution and storage	✓		△[12]	△[12]
		• Metabolism	✓			

Common issues in literature based submissions

- No or very limited search strategy provided: Without justification of excluded texts.
- No search output provided.
- Lack of provision of full text references.
- Not clear how the piece of evidence applies to/is relevant to:
  - Substance or medicine in consideration;
  - Extract type or formulation;
  - ingredient method of preparation
  - dosage;
  - frequency and duration of use;
  - route of administration;
  - therapeutic use; and/or
  - population;
- The evidence is not of appropriate scientific robustness (efficacy)





Systematic literature search – Key Take home messages

- No single literature search strategy will fit all cases and requirements will vary according to the specific nature of the application.
- Document literature search strategy with sufficient detail to ensure the strategy is logical, transparent and reproducible.
- Provide a comprehensive unbiased critical review of the available literature (including both positive and negative evidence).
- Provide full text versions (in English) of the relevant references, even if they are available from open access journals.

Website references – page 1 of 2

TGA website	www.tga.gov.au
Literature-based submissions for listed medicines and registered complementary medicines V1.0 May 2020	https://www.tga.gov.au/sites/default/files/literature-based_submissions_for_listed_medicines_and_registered_complementary_medicines_0.pdf
Pre-submission guidance for literature based submissions (LBS) | Therapeutic Goods Administration (TGA)	https://www.tga.gov.au/resources/resource/guidance/pre-submission-guidance-literature-based-submissions-lbs
ARGOM - OTC medicines – Safety and efficacy data – Section 4.1 Literature-based submissions	https://www.tga.gov.au/resources/publication/publications/otc-medicines-safety-and-efficacy-data/4-types-data-support-otc-medicine-applications
Mandatory requirements for an effective registered medicines application V1.1 July 2021	https://www.tga.gov.au/sites/default/files/mandatory-requirements-effective-registered-complementary-medicine-application.pdf
Applications for registered complementary medicines (Formerly ARGCM V8.0 Part D) V1.0 May 2020	https://www.tga.gov.au/sites/default/files/applications_for_registered_complementary_medicines_formerly_argcm_part_d.pdf
Changing a registered complementary medicine: RCM application levels and changes tables V1.0 May 2020	https://www.tga.gov.au/sites/default/files/changing_a_registered_complementary_medicine_application_levels_and_change_tables.pdf

Website references – page 2 of 2

Mandatory requirements for an application to vary the Permissible Ingredients Determination V1.0 February 2023	https://www.tga.gov.au/sites/default/files/2023-01/mandatory-requirements-for-an-application-to-vary-the-permissible-ingredients-determination.pdf
Guidance on using comparable overseas bodies reports V2.0 February 2023	https://www.tga.gov.au/sites/default/files/2022-11/guidance-using-evaluation-reports-comparable-overseas-bodies.pdf
Assessed listed medicines evidence guidelines V1.1 August 2018	https://www.tga.gov.au/sites/default/files/assessed-listed-medicines-evidence-guidelines.pdf
Guidance on using comparable overseas bodies reports V2.0 February 2023	https://www.tga.gov.au/sites/default/files/2022-11/guidance-using-evaluation-reports-comparable-overseas-bodies.pdf
Changing a listed or assessed listed medicines: application levels and change tables V2.2 March 2022	https://www.tga.gov.au/sites/default/files/changing-listed-or-assessed-listed-medicine-application-levels-and-change-tables.pdf
ARGOM - OTC application categorisation framework (Version 1.2 June 2017)	https://www.tga.gov.au/resources/publication/publications/otc-application-categorisation-framework
Changing an OTC medicine: using the Changes Tables | Therapeutic Goods Administration (TGA)	https://www.tga.gov.au/resources/publication/publications/changing-otc-medicine-using-changes-tables

Therapeutic Goods Administration (TGA)

Exhibition booth **No.1**

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Questions?

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Australian Government

Department of Health and Aged Care

Therapeutic Goods Administration