Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

Dossier requirements for literature based submissions

Guidance on required format for literature based submissions

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This guidance describes the format of literature based submissions and applies to applications based on a systematic search of the literature and those not based on a systematic search of the literature.

What format is required for literature based submissions?

A literature based submission must conform to the Common Technical Document (CTD) format, described in *CTD Module 1: Administrative information and prescribing information for Australia* and Modules 2-5 of the Common Technical Document.

When can I use literature based supporting data?

You can submit literature based data sets to satisfy the application data requirements for:

- Module 4 (nonclinical)
- Module 5 (clinical).

When can't I use literature based supporting data?

Literature based data is **not** suitable for the Module 3 (quality) component of an application, as published reports rarely include sufficient validation information.

Submit a conventional Module 3 dossier (when required) for all LBS applications.

Referencing sources in the application

- You should provide the full text of referenced publications in the dossier, not just a hyperlink, even if the document is open access on the internet at the time of submission.
- Cross-reference papers within any discussion so they can be easily located.
- Submit all references relevant to more than one CTD module within each module.

Information which does not meet the requirements for a LBS

Agency assessment reports, which are made publicly available by competent authorities for reasons of transparency, do not contain sufficient information to meet the requirements of a LBS.

Examples of these reports are:

- Australian Public Assessment Reports (AusPARs)
- European Public Assessment Reports (EPARs)
- redacted assessment reports published by the US FDA.

These documents may be submitted as supporting references.

Top of page

Requirements for each CTD Module

When replacing required study reports with literature references, ensure literature references are:

- included in the relevant Module 4 or Module 5 locations (for example, Module 4.2.3.1 Single-dose toxicity, Module 4.2.3.4 Carcinogenicity, Module 5.3.4.2 Patient PD and PK/PD Study Reports) rather than Module 4.3 Literature references or Module 5.4 Literature references
- summarised and assessed in Module 2.

"Secondary" literature references (that is, not replacing required study reports), should be:

- provided in the CTD sections for "Literature references"
- do not need to be summarised in Module 2.

You should clearly identify any studies that have been submitted within an earlier application.

Individual patient data

For a LBS, sponsors are not expected to give assurances that individual patient data are available for all published articles.

Module 1

General requirements for the preparation of Module 1 may be found in the document *CTD Module 1: Administrative information and prescribing information for Australia*.

For OTC medicines, see also the OTC dossier documents matrix.

Specific aspects involving LBSs are:

Module 1.5.1 Literature based submission documents

See TGA guidance on Module 1.5.1

The search output (Module 1.5.1.3) must be annotated to include:

- an indication as to whether the article was accepted or rejected for the application
- the reasons for inclusion/exclusion (this can be done using a legend)
- cross-referencing of articles included in the dossier.

Module 2: Overviews and summaries

Include Module 2 (overviews and summaries) - See CTD documents Module 2.

The documentation and the overviews/summaries submitted should cover all aspects of the assessment including:

- the proposed changes in the context of the newly submitted data
- previously submitted data
- registration history of the medicine.

Ensure you include:

- a review of the relevant literature, taking into account pre- and post-marketing studies
- published scientific literature including experience in the form of epidemiological studies
- all documentation, both favourable and unfavourable.

What overviews and summaries need to be provided?

Provide:

- **nonclinical overview** (Module 2.4) provides a critical analysis of the nonclinical data in the Common Technical Document
- **clinical overview** (Module 2.5) provides a critical analysis of the clinical data in the Common Technical Document
- **nonclinical summary** (Module 2.6) of the nonclinical data in the dossier
- **clinical summary** (Module 2.7) of the clinical data in the dossier.

The overviews should include:

- justifications for providing literature references instead of performing certain tests/trials
- why the references provided can replace conventional study reports and how the results presented fulfil the data requirements of a conventional application
- the rationale for selecting and excluding published papers. The eligibility criteria for inclusion of studies must be defined before there is any abstraction of data and any justification must demonstrate how each article identified by the search did or did not meet these criteria.
- an assessment of the potential for bias in the literature
- a justification if documentation is lacking.

Potential for bias in the literature

Bias may arise as a result of a number of causes including, but not limited to:

- **Publication bias** is the selective publication of studies with statistically significant results. There is a tendency for investigators to submit, and editors to accept, manuscripts for publication based on the direction or strength of the study findings.

  Attempts to find unpublished reports of studies must be outlined. Publication bias is discussed in Section 2.4 of the NHMRC handbook *How to review the evidence: systematic identification and review of the scientific literature*.
- **Outcome reporting bias** may be defined as: *the selection, on the basis of the results, of a subset of the original outcomes recorded for inclusion in publication of trials*.

  Outcomes that are statistically significant may have higher odds of being fully reported.

Overviews should discuss how the possibility of selective outcome reporting was examined, and what was found.

- **Ghost-writing** exists when any substantial contributions to an article are not acknowledged in the manuscript.

  Scientific ghost-writing, in its most serious form, refers to the practice of hiring professional scientific writers to draft articles promoting products and then procuring academic researchers as the purported authors of those articles for publication.

  The potential impact of ghost-writing on the selected articles should be discussed, especially with regard to articles which are pivotal to the application.

Time limits for preparation of overviews and summaries

The summaries and overviews must have been written not more than 12 months before lodging a PPF for a prescription medicine application or before lodging an application for an OTC medicine.

The submission of summaries and overviews outside of this time frame:

- must be justified
- may require an updated literature search and appraisal.

All submitted data/reports/papers must be cross-referenced to allow the documents to be easily located.

Authors of overviews and summaries

The authors (experts):

- do not have to be an Australian citizen or resident
- must be an expert in relation to the material being discussed.

Include information about the experts in Module 1.4.

Top of page

Modules 2.4 and 2.6 (Nonclinical overview and summary)

Comprehensively appraise:

- all information included in the application, including the extent to which the submitted data bridges the gap between the currently approved uses of the medicine the proposed uses of the medicine.

Studies conducted and reported according to internationally accepted guidelines

Include an assessment of nonclinical safety studies in terms of:

- GLP compliance
- the inherent quality of the test report or publication
- relevance to the application
- the adequacy for risk assessment.

Top of page

Modules 2.5 and 2.7 (Clinical overview and summary)

Comprehensively appraise:

- all information included in the application
- the relevance of the results with regard to Australian medical practice
- the support for any statements made about current accepted medical practice in Australia.

Selection of papers for inclusion/exclusion

- Cross-reference the discussion of the data to appropriate supporting literature, including review articles and any consensus guidelines.
- Include a relevant Cochrane review for the indication(s) sought, if it exists.

Ethics certification

Include a statement regarding Good Clinical Practice (GCP) compliance.

See *Note for Guidance on Good Clinical Practice* (CPMP/ICH/135/95) - adopted by the TGA with annotations in July 2000.

For trials conducted in Australia, applicable regulatory requirements include the *National Statement on Ethical Conduct in Human Research 2007 - Updated March 2014*.

Identify those papers where:

- ethical requirements of the study have been documented, and

- those in which the ethical conduct is either not documented or unclear.

For those papers where ethics certification is deficient, it must be stated whether or not they were conducted prior to:

- the adoption of relevant guidelines of GCP and/or
- amendments to the Declaration of Helsinki.

It is not a requirement to attempt to obtain ethics documentation; however, outline any attempts to obtain ethics documentation for the trials reported in these papers.

Appraisal of the quality of the information

Include a comprehensive appraisal of the quality of:

- all the papers submitted
- the clinical trials reported in those papers
- the data generated.

The quality of the papers included can be judged by assessing:

- their scientific impartiality, including completeness of reporting, clarity and logic of argument and
- the validity of any conclusions drawn from the study.

For questions of efficacy, the most desirable study design is always:

- randomised
- double blind
- controlled trial
- analysed by intention-to-treat (or a systematic review of several).

In cases where there are numerous published reports of such trials, it is possible to focus on these trials at the expense of other less well-designed studies. In these circumstances, the potential for bias must be addressed.

A more likely scenario may be one in which there are few published and unpublished reports available to support the application. In this case almost all papers retrieved will need to be submitted, including those of less than optimal design and conduct.

Potential duplication of data from the same patients in different articles should also be addressed.

Level of evidence

Discuss the clinical studies individually and collectively in terms of:

- the weight of evidence they provide together with a tabular and written summary of their conclusions.

A suitable checklist for assessing individual studies can be found in the *CONSORT Statement 2010*.

Levels of evidence may be described in a hierarchy such as that shown in the NHMRC publication *A guide to the development, implementation and evaluation of clinical practice guidelines* and

- Liddle J. et al (1996). *Method for evaluating research and guideline evidence. (pdf,1.29Mb)*

Designation of levels of evidence

A. NHMRC, 1999

Level	Type of evidence
I	Evidence obtained from a systematic review of all relevant randomised controlled trials.
II	Evidence obtained from at least one properly designed[1] randomised controlled trial (RCT).
III-1	Evidence obtained from well-designed pseudo-randomised controlled trials (alternate allocation or some other method), or loss of benefits of randomisation[2] .
III-2	Evidence obtained from comparative studies with concurrent controls and allocation not randomised (cohort studies), case-control studies, or interrupted time series with a control group.
III-3	Evidence obtained from comparative studies with historical control, two or more single-arm studies, or interrupted time series without a parallel control group.
IV	Evidence obtained from case series, either post-test or pre-test and post-test.

1. Implies adequate (>80%) follow-up with intention-to-treat analysis.
2. Includes inadequate (<80%) follow-up of a randomised trial, or without intention-to-treat analysis.

Top of page

B. Liddle et al, 1996

Level	Type of evidence
I-1	Systematic review of all relevant randomised controlled trials

Level	Type of evidence
I-2	Large multicentre randomised controlled trials
II	One or more randomised controlled trials and studies
III-1	Controlled trials without randomisation
III-2	Cohorts; Case-control analytic studies
III-3	Time series; Before and after studies (premeasure/postmeasure) (preferably from more than one centre or research group)
IV	Other observational studies (e.g.: case reports)
V	Opinions of respected authorities, based on their own clinical experience, or their own (non-systematic) reviews Reports of expert committees, consensus statements

An assessment of the level of evidence must include a rating according to the study type.

For example, data from randomised, double blind, controlled studies would be expected to be given greater weight than data from non-randomised, uncontrolled or open studies.

The clinical overview is expected to contain a level of evidence tabulation similar to that shown below:

Type/Level of evidence	Reference submitted	Location in dossier
Systematic review of all relevant RCT, meta-analyses (level I)	Bloggs *et al*, 1995	Module 5.3.5.3
	Smith 2010	Module 5.3.5.3

Type/Level of evidence	Reference submitted	Location in dossier
Individual properly designed RCT (level II)	Black and Brown 1993	Module 5.3.5.1
	Citizen 2003	Module 5.3.5.1
	Green *et al*, 1994	Module 5.3.5.1
	White 1996	Module 5.3.5.1
Non-randomised CT (level III-1)	Jones *et al* 1995	Module 5.3.5.1
	Brown 2007	Module 5.3.5.1
	Small *et al*, 1994	Module 5.3.5.1
Cohort or case-control analytic studies (level III-2)	None	
Case series with historical control (level III-3)	Smith and Jones, 1990	Module 5.3.5.2
Phase II study with no comparator (level IV)	Pink and Blue, 2006	Module 5.3.5.2

Pivotal studies

Indicate those clinical studies that are considered to be pivotal to the application and the reasons for doing so.

Adverse events and data

Tabulate and evaluate all adverse events relevant to the proposed change(s) in the clinical summary.

These include:

- abnormal laboratory values and drug interactions for all documented clinical studies
- any adverse events reported to the sponsor.

Discuss the data in terms of:

- overall incidence
- seriousness
- causality of effects
- dose-response relationship
- special population subgroups such as the elderly and patients with renal or hepatic impairment
- an indication of reversibility or otherwise of the adverse event.

Adverse event data should be presented in the format required in the PI* (*Form for providing product information*). The following format is preferred:

- A table of adverse events (not adverse reactions) at a cut-off of, for example, 1% comparing the frequency of adverse events (n(%) or (%)) on drug with placebo/active comparator (if studies support this comparison) (usually very common and common)
- A line listing of adverse reactions that fall below the cut-off by System Organ Classes (SOC) using CIOMS frequencies (usually uncommon, rare)
- A post-marketing section of adverse reactions by system organ class using CIOMS frequencies (usually rare or very rare).

**For OTC medicines, this would only be required where the medicine was required to have a PI.*

Formulation

Ensure the clinical overview:

- comments on the formulations used in the studies
- discusses the possible implications of differences between the formulations reported in the literature.

Special populations

Provide bibliographic data to support claims of efficacy, safety and any other issues relevant to any special populations affected by the proposed changes.

The clinical summary should place particular importance on evaluating the relevance of the results with respect to:

- The population(s) affected by the proposed registration or
- changes in the PI.

Top of page

Module 3: Quality data

Literature based data sets are not suitable for the quality (Module 3) component of an application, as published reports rarely include sufficient validation information.

A conventional Module 3 dossier should therefore be submitted for all LBS applications.

Module 4: Safety (Nonclinical) data

Nonclinical data would normally be expected to consist of individual test reports:

- conducted and reported according to internationally accepted guidelines
- in compliance with the principles of good laboratory practice (GLP).

However, when appropriately justified, it may be supported by:

- published literature
- review articles.

Module 5: Efficacy (Clinical) data

Efficacy data included in a LBS may comprise:

- published literature including primary reports
- systematic overviews
- unpublished study reports and papers, and/or company data
- consensus guidelines and supporting documentation from professional bodies, including documentation and data used to derive the consensus guidelines (the primary data used to derive consensus guidelines must always be included).

Submit all reports with regard to clinical safety data, including:

- published or unpublished reports
- individual case reports
- overviews relevant to the proposed change(s)
- scientific reports not suitable for efficacy assessment due to poor trial design or inadequate analysis, but providing safety data about the product.

Note: It is not acceptable to provide only published literature in support of an application where company study reports exist.

Other clinical safety data may include:

- company generated post-marketing surveillance reports (PSUR) for:
    - the proposed indication, if the medicine has been marketed for that indication overseas
    - general marketing overseas and in Australia

  Wherever possible, the data should be stratified according to population groups affected by any proposed change (for example, by age, ethnicity etc).
- reports from the Advisory Committee on the Safety of Medicines (ACSOM) and its predecessor the Adverse Drug Reactions Advisory Committee (ADRAC)
- reports from relevant international sources, for example, the WHO Program for International Drug Monitoring.

Top of page

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