



Australian Government

Department of Health

Therapeutic Goods Administration

# Mandatory requirements for an effective registered complementary medicine application

For applications lodged from March 2018

Version 1.1, July 2021

**TGA** Health Safety  
Regulation



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# 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 register a complementary medicine to be considered effective and proceed to evaluation.

## Scope

These requirements apply to applications to register a complementary medicine that are lodged with the TGA from March 2018, including applications to change a registered complementary medicine (RCM) 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

### Applications for new registrations

Applications for new registrations<sup>1</sup> are made under [Section 23 of the Act](#). Section 23 requires that applications:

- are made in accordance with a form or in a manner approved by the Secretary (subsection 23(1) of the Act)
- include such information in a form approved by the Secretary as will allow the determination of the application (paragraph 23(2)(b) of the Act); and
- for restricted medicines, include product information in the form approved under section 7D of the Act (paragraph 23(2)(ba) of the Act).

### Section 23 instruments

The [Section 23 instruments](#) specify how applications to register a complementary medicine must be made and require applications to include the information described in the following regulatory documents in order to be effective and proceed to evaluation:

- Mandatory requirements for an effective registered complementary medicine application (this document)
- [CTD Module 1: registered complementary medicines](#).

### Registered complementary medicine applications

For information on the RCM application levels that are referred to in this document, and the application process, go to:

- [An overview of the regulation of complementary medicines in Australia](#)

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<sup>1</sup> A new registration is one that requires a new ARTG entry by reason of being separate and distinct goods under section 16 of the *Therapeutic Goods Act 1989*. This includes new chemical entities, new strengths, new dosage forms, different directions for use, formulation changes, changes in trade name, extension of indication etc. Under the Therapeutic Goods (Groups) Order No. 1 of 2001, not all new registrations will result in a new AUST R number being allocated if the existing medicine is 'grouped' with the new medicine.

- [Complementary medicine registration process](#)
- [Determining the correct application level for RCM medicine submissions](#) (Application Categories RCM1 to RCM5)
- [Process to change a registered complementary medicine](#) (CN to C4)
- [Complementary medicines changes tables](#)
- Mandatory requirements for an effective application (this document)

# 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: registered complementary medicines](#) completed to the extent that it is applicable for all RCM application levels.
- Module 2: [Overviews, written summaries and tabulated summaries of the data](#) contained in the Modules 3, 4 and 5. Completed to the extent that it is applicable for particular RCM3, RCM4, RCM5, C3-RCM and C4-RCM applications, as detailed in [Appendix A: Specific mandatory requirements \(Module 2\)](#).
- Module 3: [ICH M4Q Common technical document for the registration of pharmaceuticals for human use - Quality \(CPMP/ICH/2887/99 Rev 1 Quality\)](#). Completed to the extent that it is applicable for particular RCM1, RCM2, RCM3, RCM4, RCM5, and C2-RCM applications, as detailed in [Appendix A: Specific mandatory requirements \(Module 3\)](#).
- Module 4: [ICH M4S Common technical document for the registration of pharmaceuticals for human use - Safety \(CPMP/ICH/2997/99 Rev 1 Safety\)](#). Completed to the extent that it is applicable for particular RCM4, RCM5, C3-RCM and C4-RCM applications, as detailed in [Appendix A: Specific mandatory requirements \(Module 4\)](#).
- 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 RCM4, RCM5, C3-RCM and C4-RCM applications, as detailed in [Appendix A: Specific mandatory requirements \(Module 5\)](#).

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 registration on the Australian Register of Therapeutic Goods (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 2, 3, 4 and 5 for an application to be considered effective is at [Appendix A – Specific technical data requirements](#).

For more information about the modules 2, 3, 4 and 5 see [Common Technical document \(CTD\)](#).



## 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 to demonstrate quality, safety, and efficacy. If the dossier does not contain all of this information, the TGA may not be able to determine whether the quality, safety and efficacy of the medicine has been satisfactorily established.

### Please note



The TGA has an ongoing process to consider newly released and updated EU and ICH guidelines and decide whether or not to adopt them. 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 and 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 come to a view as to whether the medicine can be registered on 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 specific technical requirement or does not 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:

- the requirement, guideline or part of the guideline that is not being met must be identified and explain how it is not being met
- detail of the proposed alternative approach and a contemporary scientific justification for why the approach is valid, with reference to supporting documents
- citations of the relevant reference documents, including TGA documents, where appropriate
- literature based submissions must be in accordance with [TGA guidance on Literature based submissions](#); and
- copies of all cited references documents (other than TGA documents) in the dossier.

## **Purpose of the justification**

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 23 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 registered in the ARTG. The content and merit of a justification (i.e. whether the alternative approach is in fact valid) will be assessed during the evaluation phase.

## **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: registered complementary medicines](#)
- [General dossier requirements](#)
- the approved Non Prescription Medicine application form in [TGA Business Services](#)

## Appendix A - Specific mandatory requirements

### Requirements for RCM 1 applications:

- CTD Module 1: registered complementary medicines including:
  - a letter of authorisation from the sponsor of the fully evaluated originator medicine to access the medicine information in Module 1 under 'letters of authorisation' (1.5.5); and
  - assurance that all quality aspects of the proposed medicine are identical to the originator medicine, other than differences that are specifically permitted (as listed in the [permitted differences guidance](#)) in Module 1 under 'Assurances' (1.5.7)
- If the proposed product includes a new flavour, fragrance or colour (including printing inks), provide the proposed specifications and details of the test methods for the new flavour/fragrance/colours(s) in Module 3 under 'control of excipients' (3.2.P.4).

### Requirements for RCM 2 applications:

- [CTD Module 1: registered complementary medicines](#) including:
  - Copies of Comparable Overseas Regulator (COR)<sup>2</sup> evaluation reports in Module 1 under 'Foreign regulatory information' (1.11)

### Requirements for RCM 3 applications:

- [CTD Module 1: registered complementary medicines](#):
  - 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).
- Submit the relevant technical module out of Module 3, Module 4 and Module 5.

### Requirements for RCM 4 applications:

- [CTD Module 1: registered complementary medicines](#)
- Module 2
- Submit the relevant technical modules out of Module 3, Module 4 and Module 5.

### Requirements for RCM 5 applications:

- [CTD Module 1: registered complementary medicines](#)
- Module 2
- Module 3
- Module 4
- Module 5.

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<sup>2</sup> TGA is currently developing guidance for the use of evaluation reports from CORs. A list of approved CORs will be available on the TGA website in due course.

## Table 1: Module 2 - CTD Summaries

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.

CTD Module	RCM Application level	Requirement	Table reference number
2.3 Quality overall summary	RCM4 (when M3 is required) and RCM5	Provide Module 2.3 completed in accordance with <a href="#">ICH M4Q Common technical document for the registration of pharmaceuticals for human use - Quality (CPMP/ICH/2887/99 Rev 1 Quality)</a> .	1.a
2.4 Nonclinical overview	RCM4 (when M4 is required) and RCM5	For all applications that include Module 4, provide Module 2.4 completed in accordance with <a href="#">ICH M4S Common technical document for the registration of pharmaceuticals for human use - Safety (CPMP/ICH/2887/99 Rev 1 Safety)</a> .  Also provide Module 2.4 for applications where the levels of impurities and degradants lie outside the levels permitted in <a href="#">Quality data for complementary medicines</a> (these applications require Module 4 data in support of the proposed limits or a justification for the absence of Module 4 data).	1.b
2.5 Clinical overview	RCM5 and when M5 data is required for RCM4, C3-RCM and C4-RCM	For all applications that include Module 5, provide Module 2.5 completed in accordance with <a href="#">ICH M4E Common technical document for the registration of pharmaceuticals for human use - Efficacy (CPMP/ICH/2887/99 Rev 1 Efficacy)</a> 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 from the bioequivalence study together with any other relevant information, as appropriate.	1.c
2.6 Nonclinical summary	C3-RCM, C4-RCM (only applicable when M4 data is required)	For all applications that include Module 4, provide Module 2.6 completed in accordance with <a href="#">ICH M4S Common technical document for the registration of pharmaceuticals for human use - Safety (CPMP/ICH/2887/99 Rev 1 Safety)</a> .	1.d
2.7 Clinical summary	C3-RCM, C4-RCM (only applicable when M5 data is required)	For all applications that include Module 5, provide Module 2.7 completed in accordance with <a href="#">ICH M4E Common technical document for the registration of pharmaceuticals for human use - Efficacy (CPMP/ICH/2887/99 Rev 1 Efficacy)</a> 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 2.7 would consist of a clinical summary of the bioequivalence study.	1.e

## Table 2: Module 3 - Quality

The table below describes the minimum data that must be submitted in Module 3 for an application to be considered effective. For further guidance refer to the [Quality information for a new registered complementary medicine](#).

CTD Module	RCM Application level	Module 3 requirement	Table reference number
3.2.S Drug Substance	RCM5 – new active ingredient	For an application to register a medicine containing a new chemical entity that is an active ingredient, provide Module 3.2.S data in accordance with the <a href="#">Quality data for complementary medicines</a> .	2.a
3.2.S.4 Control of Drug substance	RCM3, RCM4, RCM5 – excluding new active ingredients and premixes	<p>For a drug substance that is the subject of a default standard monograph provide, either:</p> <ul style="list-style-type: none"> <li>confirmation that the full specifications (test methods and limits) detailed in the relevant monograph in the default standard (BP/Ph.Eur or USP) are applied and no additional critical control parameter tests are necessary to ensure the quality of the medicine, e.g. particle size of the active for inclusion in a suspension; or</li> <li>the proposed drug substance specifications; and: <ul style="list-style-type: none"> <li>a justification for any non-pharmacopeial tests and limits</li> <li>details of non-pharmacopeial test methods.</li> </ul> </li> </ul> <p>For a drug substance that is NOT the subject of a default standard monograph provide:</p> <ul style="list-style-type: none"> <li>the proposed drug substance specifications; and: <ul style="list-style-type: none"> <li>a justification for the tests and limits</li> <li>details of the test methods.</li> </ul> </li> </ul>	2.b

CTD Module	RCM Application level	Module 3 requirement	Table reference number
3.2.S.4 Control of drug substance	RCM3, RCM4, RCM5 – premixes (ingredient blends) <sup>3</sup>	<p>For a drug substance that is purchased already manufactured as part of an ingredient blend or premix, provide:</p> <ul style="list-style-type: none"> <li>the finished product manufacturer's acceptance specifications for the ingredient blend or premix</li> <li>a justification for the tests and limits</li> <li>confirmation that all components of the blend or premix are of appropriate pharmaceutical grade and comply with any relevant default standards.</li> </ul>	2.c
3.2.P.1 & 3.2.P.2 Drug product (description, composition and pharmaceutical development)	RCM3, RCM4, RCM5	<ul style="list-style-type: none"> <li>Define the composition of the medicine and role of the ingredients.</li> <li>Provide details and a justification for any overage applied during manufacture.</li> <li>If tablets are scored, provide data to confirm that splitting is clean and the portions produced comply with pharmacopoeial limits for uniformity of weight/content.</li> <li>Provide full details of pharmaceutical development for: <ul style="list-style-type: none"> <li>modified release dosage forms</li> <li>RCM5 applications for new strengths, new dosage forms, new fixed combination medicines or new chemical entities.</li> </ul> </li> </ul>	2.d

<sup>3</sup> For more information on proprietary ingredient mixtures that contain an active ingredient see [Streamlining proprietary ingredient categories](#).

CTD Module	RCM Application level	Module 3 requirement	Table reference number
3.2.P.3  Drug product (manufacture)	RCM3, RCM4, RCM5	<p>Include a brief outline of the method of manufacture and batch formula.</p> <p>Provide an assurance that the manufacturing process will be validated (or has been validated) according to the requirements of the Code of Good Manufacturing Practice [the <a href="#">Therapeutic Goods (Manufacturing Principles) Determination 2018</a> contains a definition of 'the Code'], and that the manufacturer's validation report and related information will be available for review, on request, by the TGA within 3 months of release for supply of the first production batch.</p> <p>Additional manufacturing validation information is required for the following specific medicine types:</p> <ul style="list-style-type: none"> <li>• for oral dosage forms where the active ingredient is present at less than 2 mg or 2% w/w (micro dose) the full manufacturer's process validation report must be provided</li> <li>• for novel dosage forms and sustained release medicines (excluding enteric coated medicines) provide the manufacturer's process validation report (or a summary of the report) including the critical steps in the manufacturing process and the manufacturer's analysis and conclusions.</li> </ul>	2.e
3.2.P.4  Control of excipients	RCM1 (flavour/fragrance/colour variants only)  C2-RCM change code GPI - addition of flavour/fragrance/colour.	Provide the proposed specifications and details of the test methods for the new flavour/fragrance/colour.	2.f

CTD Module	RCM Application level	Module 3 requirement	Table reference number
3.2.P.4 Control of excipients	RCM3, RCM4, RCM5	<p>State which excipients comply fully with the applicable monograph in the default standard (BP, Ph.Eur. or USP).</p> <p>For excipients that are the subject of a default standard monograph, provide either:</p> <ul style="list-style-type: none"> <li>confirmation that the <b>full</b> specifications (test methods and limits) detailed in the relevant monograph in the default standard (BP, Ph.Eur or USP) are applied and no additional critical control parameter tests are necessary to ensure the quality of the medicine; or</li> <li>the proposed specifications; and: <ul style="list-style-type: none"> <li>a justification for any non-pharmacopoeial tests and limits</li> <li>details of non-pharmacopoeial test methods.</li> </ul> </li> </ul> <p>For excipients that are NOT the subject of a default standard monograph, provide:</p> <ul style="list-style-type: none"> <li>the proposed specifications; and: <ul style="list-style-type: none"> <li>a justification for the tests and limits</li> <li>details of the test methods.</li> </ul> </li> </ul> <p>For excipients that are purchased already manufactured as part of a premix (ingredient blend), provide:</p> <ul style="list-style-type: none"> <li>the finished product manufacturer's acceptance specifications</li> <li>a justification for the tests and limits</li> <li>confirmation that all components of the blend or premix are of appropriate pharmaceutical grade and comply with any relevant default standards.</li> </ul>	2.g



CTD Module	RCM Application level	Module 3 requirement	Table reference number
3.2.P.5.1 Control of drug product	RCM2, RCM3, RCM4, RCM5	Provide the proposed expiry and release specifications for the finished product.  <b>Note:</b> Finished product specifications must be provided for all RCM2, RCM3, RCM4, RCM5 applications, including those where a justification is made for providing an abridged Module 3 (for example, when all quality aspects are identical to a fully evaluated 'parent' medicine, whose sponsor has given the TGA authorisation to access the parent files for the purpose of the application).	2.h
3.2.P.5.2 Analytical procedures	RCM3, RCM4, RCM5	Provide a detailed description of all in-house test methods, in accordance with the requirements of the <a href="#">Quality data for complementary medicines – Analytical procedures</a> .	2.i
3.2.P.5.3 Validation of test methods	RCM3, RCM4, RCM5	Provide analytical validation reports for critical assay methods, in accordance with the requirements of the <a href="#">Quality data for complementary medicines – Analytical procedures</a> .  All raw data supplied (e.g. HPLC traces) must be clear and legible.	2.j
3.2.P.5.4 Batch analysis	RCM2, RCM3, RCM4, RCM5	Provide certificates of analysis for at least two batches.	2.k
3.2.P.5.6 Control of drug product	RCM3, RCM4, RCM5	Provide a justification for the finished product specifications including: <ul style="list-style-type: none"> <li>a justification in terms of safety for any impurity limits that are above those specified in the <a href="#">Quality data for complementary medicines</a> (refer to Table 1 and Table 3 for the relevant Module 2.4 and Module 4 requirements).</li> </ul> <b>Note:</b> The finished product specifications must ensure compliance with all applicable default standard requirements and <a href="#">Therapeutic Goods Orders</a> .	2.l

CTD Module	RCM Application level	Module 3 requirement	Table reference number
3.2.P.7 Container closure system	RCM2, where a measuring device is supplied with the medicine.	Provide details of the calibrations on the measuring device.	2.m
3.2.P.7 Container closure system	RCM3, RCM4, RCM5	<ul style="list-style-type: none"> <li>Provide details of the container and measuring or dose delivery devices, including: <ul style="list-style-type: none"> <li>details of the materials and specifications</li> <li>technical drawings of dose delivery/measuring device, where design, composition and performance of the device is not clearly described in the submitted specifications (including details of the calibrations).</li> </ul> </li> <li>For plastic and rubber packaging components of the primary packaging provide evidence that the components comply with relevant BP/Ph. Eur and/or USP/NF requirements for polymeric materials used in packaging medicines or, if appropriate, are approved for use with foodstuffs.</li> <li>If the medicine is subject to the <a href="#">Therapeutic Goods Order No 80 Child-resistant Packaging Requirements for Medicines (TGO 80)</a> provide an assurance that the container closure system complies TGO 80.</li> <li>For medicines supplied with a measuring device, provide an assurance that it complies with the requirements for <i>Uniformity of Weight (Mass) of Delivered Doses from Multidose Containers</i> in the BP/Ph.Eur Appendix XII C. <i>Consistency of Formulated Preparations</i>.</li> </ul>	
3.2.P.8 Stability	RCM3, RCM4, RCM5	<p>Provide information regarding stability trials in accordance with the requirements of the <a href="#">Quality data for complementary medicines</a>, including:</p> <ul style="list-style-type: none"> <li>a tabular stability summary and conclusions in regard to the storage conditions and shelf-life</li> </ul>	2.o

CTD Module	RCM Application level	Module 3 requirement	Table reference number
		<ul style="list-style-type: none"> <li>• a statement of which batches are identical to those intended for marketing in terms of formulation, container, and manufacture. Provide details and justification for any differences between the stability batches and the proposed medicine</li> <li>• a post-approval stability commitment to conduct full term stability testing on at least two production batches (if required)</li> <li>• full details of stability testing conducted on each individual strength, container type and size of the medicine (unless bracketing or matrixing is applied), in accordance with the relevant CPMP/ICH guidelines and associated TGA annotations.               <ul style="list-style-type: none"> <li>– Results must be in tabular format.</li> <li>– Confirm that the test methods used in the stability study are the same as those provided in 3.2.P.5 Control of the Drug Product or, if this is not the case, provide detailed stability study test methods and analytical validation data.</li> <li>– If there were any changes in test procedures during the course of the trials, provide comparison and correlation of results generated by the alternative methods.</li> <li>– For conventional dosage forms where the active ingredient is known to be stable, provide no less than 6 months long term and accelerated stability data on a minimum of two batches of at least pilot scale.</li> <li>– For unconventional dosage forms (including modified release) or for medicines that are likely to be unstable or contain a new active ingredient, provide no less than 12 months long term and 6 month accelerated stability data on a minimum of three batches, of which two must be at least pilot scale.</li> <li>– Provide results of microbiological contamination testing or, where relevant, sterility testing.</li> <li>– For solid dosage forms in potentially moisture-permeable packaging, provide high humidity stability data.</li> </ul> </li> </ul>	

CTD Module	RCM Application level	Module 3 requirement	Table reference number
		<ul style="list-style-type: none"> <li>– For non-solid dosage forms in potentially moisture-permeable packaging, provide low humidity stability data.</li> <li>– For multi-dose liquid or semi-solid medicines provide: <ul style="list-style-type: none"> <li>▪ antimicrobial preservative efficacy data at the beginning and end of the closed shelf life, as specified in TGO 77 Microbiological Standards for Medicines</li> <li>▪ information to support the in-use period e.g. microbiological challenge testing/simulated use testing.</li> </ul> </li> </ul> <p>If the stability data package does not meet any or all of the above requirements, this must be identified in the application cover letter and a justification must be included that meets the requirements detailed above in <a href="#">Justification for not complying with technical data requirements</a>.</p>	

**Table 3: Module 4 - Safety (nonclinical study reports)**

Application type (more than one type may apply)	RCM Application level	CTD Module	Module 4 requirement	Table reference number
<p>Application for a medicine that contains an excipient that is one or more of:</p> <ul style="list-style-type: none"> <li>a new chemical entity (i.e. not on the TGA Ingredient tables)</li> <li>not approved for use in listed complementary medicines</li> <li>at a higher concentration or daily dose than has been approved for that route of administration; and/or</li> <li>is proposed for a new route of administration.</li> </ul> <p><b>Note:</b> If you are unsure whether the excipient has been assessed for the proposed route of administration, concentration or RCM use, contact <a href="mailto:complementary.medicines@health.gov.au">complementary.medicines@health.gov.au</a></p>	RCM4. RCM5. C3-RCM	4	<p>Provide nonclinical data or a justification for not providing data, in accordance with the:</p> <ul style="list-style-type: none"> <li><a href="#">Safety and efficacy information for complementary medicines</a></li> </ul> <p>An assessment of the information relating to safety must be provided in the nonclinical overview (Module 2.4).</p>	3.a
<p>Application for a medicine that has impurities that are above those allowed in <a href="#">Impurities and incidental constituents of complementary medicines</a></p>	RCM4, RCM5	4	<p>Provide safety data (Module 4) or a scientific justification (Module 2.4 and/or Module 4) to support the proposed impurity limits.</p> <p>Provide an assessment of this information in the nonclinical overview (Module 2.4).</p>	3.b

Application type (more than one type may apply)	RCM Application level	CTD Module	Module 4 requirement	Table reference number
Applications that are fully or partly literature based (literature based submission).	RCM4, RCM5, C3-RCM, C4-RCM	4.3	Provide information in accordance with the TGA guidance: <ul style="list-style-type: none"> <li><a href="#">Literature based submissions</a></li> <li><a href="#">Safety and efficacy information for complementary medicines</a></li> </ul> Note that Modules 1.5.1, 2.4 and 2.6 (as applicable) are also required.	3.c
Applications for a topical medicine that includes a 'hypoallergenic' claim.	RCM4, RCM5	4	Provide data in accordance with the requirements detailed in the <a href="#">Guidelines on OTC applications for specific substances – Hypoallergenicity of topical preparations</a> .	3.d
Application for a non-generic medicine that has one or more of: <ul style="list-style-type: none"> <li>a new chemical entity that is an active ingredient new salt or ester</li> <li>a new combination of active ingredients</li> <li>a new route of administration of the active ingredient</li> <li>higher dosages (strength) of the active ingredient or use over a longer period of time</li> <li>a different patient population</li> </ul>	RCM4, RCM5, C4-RCM	4	Provide nonclinical data or a scientific justification for the absence of nonclinical data, in accordance with: <ul style="list-style-type: none"> <li><a href="#">Module 4: Safety (non-clinical study reports)</a></li> <li><a href="#">Safety and efficacy information for complementary medicines</a></li> </ul> Provide an assessment of the information relating to safety in the nonclinical overview (Module 2.4) or nonclinical summary (Module 2.6).	3.e

## Table 4: Module 5 - Efficacy (clinical study reports): General application requirements

In addition to the requirements in this table, the specific Module 5 requirements for generic medicine applications are described in Table 5, and for non-generic medicine applications in Table 6.

Application type (more than one type may apply)	RCM Application level	CTD Module	Module 5 Requirement	Table reference number
Applications that include comparative bioavailability/ bioequivalence reports	RCM4, RCM5, C4-RCM	5.3.1	<p>Provide bioavailability/bioequivalence study reports in accordance with requirements detailed in:</p> <ul style="list-style-type: none"> <li><a href="#">Guidance 15: Biopharmaceutical Studies</a></li> </ul> <p><b>Note:</b></p> <ul style="list-style-type: none"> <li>The Australian originator reference medicine used in the studies must have been registered on the basis of a full dossier, which may include chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data.</li> <li>The bioavailability/bioequivalence summary is placed in Module 1.9.1</li> </ul>	4.a
Applications that include reports of biopharmaceutic studies using overseas reference product	RCM4, RCM5, C4-RCM	5.3.1	<p>For a biopharmaceutic study using an overseas reference product, provide data in accordance with requirements detailed in <a href="#">Guidance 15: Biopharmaceutic studies – Choice of the reference product for bioequivalence of generic medicines</a>.</p>	4.b
Applications that are fully or partly literature based (literature based submission)	RCM4, RCM5, C4-RCM	5.4	<p>Provide information in accordance with the TGA guidance:</p> <ul style="list-style-type: none"> <li><a href="#">Literature based submissions</a></li> <li><a href="#">Safety and efficacy information for complementary medicines</a></li> </ul> <p><b>Note:</b> Module 1.5.1, 2.5 and Module 2.7 and copies of all references will need to be provided.</p>	4.c



Application type (more than one type may apply)	RCM Application level	CTD Module	Module 5 Requirement	Table reference number
Applications for locally acting, locally applied medicines that include studies using pharmacodynamic endpoints	RCM4, RCM5, C4-RCM	5	Provide data demonstrating that the pharmacodynamic model is internally and externally valid. The use of pharmacodynamic endpoints must be justified in terms of their direct relevance to the intended therapeutic effect of the active ingredient in the medicine.	4.d

**Table 5: Module 5 - Efficacy (clinical study reports): RCM4 application requirements (generic medicines)**

Application type (more than one type may apply)	RCM Application level	CTD Module	Module 5 requirement	Table reference number
Generic oral medicines, other than those specifically excluded from requiring bioequivalence data see Guidance 15 - Medicines that do not require biopharmaceutical data	RCM4	5.3.1	Provide bioavailability/bioequivalence study reports in accordance with the requirements for generic medicines detailed in: <ul style="list-style-type: none"> <li><a href="#">Generic registered complementary medicines</a></li> <li><a href="#">Safety and efficacy information for complementary medicines</a></li> <li><a href="#">Guidance 15: Biopharmaceutical Studies</a></li> </ul>	5.a
Generic modified release oral medicine	RCM4	5.3.1	Provide the bioavailability/bioequivalence study reports in accordance with the requirements detailed in: <ul style="list-style-type: none"> <li><a href="#">Guidance 15: Biopharmaceutical Studies</a></li> <li><a href="#">Guideline in the investigation of bioequivalence</a></li> <li><a href="#">Safety and efficacy information for complementary medicines</a></li> <li><a href="#">Guidance on the pharmacokinetic and clinical evaluation of modified release dosage forms (EMA/CPMP/EWP/280/96 Corr 1)</a></li> </ul>	5.b
Generic topical medicines	RCM4	5.3.4 5.3.5	Provide data demonstrating therapeutic equivalence with a corresponding Australian originator medicine, in accordance with the requirements detailed in: <ul style="list-style-type: none"> <li><a href="#">Generic registered complementary medicines</a></li> <li><a href="#">Safety and efficacy information for complementary medicines</a></li> </ul>	5.c

Application type (more than one type may apply)	RCM Application level	CTD Module	Module 5 requirement	Table reference number
Generic antiseptic for: <ul style="list-style-type: none"> <li>First aid</li> <li>Use in the mouth</li> </ul>	RCM4	5.3	Provide <i>in vitro</i> data demonstrating the antimicrobial activity using the following suitable test methods (as relevant): <ul style="list-style-type: none"> <li>the <i>in vitro</i> test described in the <a href="#">FDA Tentative Final Monograph for first aid antiseptic products</a></li> <li><a href="#">TGA disinfectant test (option D) for antiseptics</a> modified to make it a quantitative method and supported by adequate validation data</li> <li><a href="#">FDA Tentative Final Monograph for oral antiseptic drug products</a></li> <li><a href="#">FDA proposed monograph for antigingivitis /antiplaque drug products</a></li> </ul>	5.d
Generic antiseptic: <ul style="list-style-type: none"> <li>Handwashes or handrubs</li> </ul>	RCM4	5.3	Provide <i>in vitro</i> and <i>in vivo</i> data demonstrating the efficacy using the following suitable test methods (as relevant): <ul style="list-style-type: none"> <li>The European Standard EN13727 for chemical disinfectants and antiseptics</li> <li><a href="#">FDA Tentative Final Monograph for health-care antiseptic drug products</a></li> <li>The European Standard EN 1499 for hygienic handwashes</li> <li>The European Standard EN 1500 for hygienic handrubs</li> <li>The European standard EN 12791 for surgical hand disinfectants</li> </ul>	5.e

Application type (more than one type may apply)	RCM Application level	CTD Module	Module 5 requirement	Table reference number
Generic head lice treatment	RCM4	5.3	Provide data in accordance with: <ul style="list-style-type: none"> <li><a href="#">Guidelines on OTC applications for specific substances – Headlice treatments</a></li> <li><a href="#">Safety and efficacy information for complementary medicines</a></li> </ul>	5.f
Any other generic medicines	RCM4	5.3	Provide data demonstrating therapeutic equivalence with a corresponding Australian originator medicine, in accordance with the requirements detailed in: <ul style="list-style-type: none"> <li><a href="#">Generic registered complementary medicines</a></li> <li><a href="#">Safety and efficacy information for complementary medicines</a></li> </ul>	5.g

**Table 6: Module 5 - Efficacy (clinical study reports): RCM5 and C4-RCM application requirements (for new non-generic medicines to be registered in the ARTG)**

Application type (more than one type may apply)	RCM Application level	CTD Module	Module 5 requirement	Table reference number
New strength	RCM5	5	<ul style="list-style-type: none"> <li>For medicines that are systemically absorbed (e.g. oral tablets), provide comparative bioavailability/bioequivalence study reports in accordance with <a href="#">Guidance 15: Biopharmaceutic Studies</a>.</li> <li>For locally applied, locally acting medicines, provide data in accordance with the EU document <a href="#">Clinical requirements for locally applied, locally acting products containing known constituents</a>.</li> </ul>	6.a
New dosage form	RCM5	5	<p>Provide data in accordance with:</p> <ul style="list-style-type: none"> <li>the guidance <a href="#">Safety and efficacy information for complementary medicines</a></li> <li>any other specific Australian or EU guidelines relevant to the medicine.</li> </ul> <p>For systemically absorbed dosage forms provide study reports in accordance with <a href="#">Guidance 15: Biopharmaceutic Studies</a>.</p>	6.b
New modified release dosage forms	RCM5	5	<p>Provide data in accordance with:</p> <ul style="list-style-type: none"> <li>the guidance <a href="#">Safety and efficacy information for complementary medicines</a></li> <li>any other specific Australian or European Union (EU) guidelines relevant to the medicine, including the <a href="#">Guidance on the pharmacokinetic and clinical evaluation of modified release dosage forms (EMA/CPMP/EWP/280/96 Corr 1)</a></li> </ul>	6.c

Application type (more than one type may apply)	RCM Application level	CTD Module	Module 5 requirement	Table reference number
New route of administration	RCM5	5	Provide data in accordance with: <ul style="list-style-type: none"> <li>the guidance <a href="#">Safety and efficacy information for complementary medicines</a></li> <li>any other specific Australian or EU guidelines relevant to the medicine.</li> </ul>	6.d
New indications, dosage, directions for use or target population	RCM5, C4-RCM (change code GID or GDD)	5	Provide data in accordance with: <ul style="list-style-type: none"> <li>the guidance <a href="#">Safety and efficacy information for complementary medicines</a></li> <li>any other specific Australian or EU guidelines relevant to the medicine.</li> </ul>	6.e
New fixed combination medicine or composite packs containing multiple active ingredients that do not contain a new active ingredient (new chemically entity)	RCM5	5	Provide data in accordance with: <ul style="list-style-type: none"> <li>the guidance <a href="#">Safety and efficacy information for complementary medicines</a></li> <li><a href="#">Complementary medicines presented as composite packs or kits</a></li> <li>any other specific Australian or European Union (EU) guidelines relevant to the medicine, including the <a href="#">Guideline on Clinical Development of Fixed Combination Medicinal Products (CPMP/EWP/240/95 Rev 1)</a>, adopted by the TGA.</li> </ul>	6.f

Application type (more than one type may apply)	RCM Application level	CTD Module	Module 5 requirement	Table reference number
Non-generic locally applied, locally acting medicine (e.g. topical medicine)	RCM5	5	<p>Provide data in accordance with:</p> <ul style="list-style-type: none"> <li>the guidance <a href="#">Safety and efficacy information for complementary medicines</a></li> <li>any other specific Australian or European Union (EU) guidelines relevant to the medicine, including the guideline <a href="#">Clinical requirements for locally applied, locally acting products containing known constituents</a></li> </ul>	6.g
Non-generic antiseptic	RCM5	5	<p>Provide <i>in vitro</i> and <i>in vivo</i> data demonstrating the efficacy using the following suitable test methods (as relevant):</p> <ul style="list-style-type: none"> <li>The <i>in vitro</i> test described in the <a href="#">FDA Tentative Final Monograph for first aid antiseptic products</a></li> <li>The <a href="#">TGA disinfectant test (option D) for antiseptics</a> modified to make it a quantitative method and supported by adequate validation data</li> <li>The <a href="#">FDA Proposed Rule for oral antiseptic drug products</a></li> <li><a href="#">FDA proposed monograph for antigingivitis /antiplaque drug products</a></li> <li>The European Standard EN13727 for chemical disinfectants and antiseptics</li> <li><a href="#">FDA Tentative Final Monograph for health-care antiseptic drug products</a></li> <li>The European Standard EN 1499 for hygienic handwashes</li> <li>The European Standard EN 1500 for hygienic handrubs</li> </ul>	6.h



Application type (more than one type may apply)	RCM Application level	CTD Module	Module 5 requirement	Table reference number
Non-generic head lice treatment	RCM5	5	Provide data in accordance with: <ul style="list-style-type: none"> <li><a href="#">Guidelines on OTC applications for specific substances – Head lice treatments</a></li> </ul>	6.i
New active ingredient (new chemical entity)	RCM5	5	Provide data in accordance with the following studies (or a robust scientific justification for not including such studies): <ul style="list-style-type: none"> <li>absolute bioavailability study (the extent of the absorption of a non-intravenous dose compared to intravenous administration of the same substance)</li> <li>study to establish that the proposed formulation is optimal (e.g. a study versus an oral solution of the drug)</li> <li>bioequivalence studies between the proposed registration formulation and pivotal clinical trial formulations</li> <li>bioequivalence studies amongst the various strengths proposed for registration (if applicable)</li> <li>a food effect study; and</li> <li>any other specific Australian or European Union (EU) guidelines relevant to the medicine, including: <ul style="list-style-type: none"> <li>for topical medicines provide safety and efficacy data in accordance with the EU guidance <a href="#">Clinical requirements for locally applied, locally acting products containing known constituents</a></li> <li>for modified release medicines provide safety and efficacy data in accordance with the EU <a href="#">Note for guidance on modified release and transdermal dosage forms: Section II</a></li> </ul> </li> </ul>	6.j

Application type (more than one type may apply)	RCM Application level	CTD Module	Module 5 requirement	Table reference number
			<p><a href="#"><i>(Pharmacokinetics and clinical evaluation)</i></a>  <a href="#"><i>(CPMP/EWP/280/96)</i></a></p> <p>– for fixed combination medicines or composite packs provide safety and efficacy data in accordance with the EU <a href="#"><i>Guideline on Clinical Development of Fixed Combination Medicinal Products</i></a> (CPMP/EWP/240/95 Rev 1), adopted by the TGA.</p>	

## Version history

Version	Description of change	Author	Effective date
V1.0	Original publication	Complementary and Over the Counter Medicines Branch	March 2018
V1.1	Minor addition of footnote to Table 2: Module 3 – Quality	COMB	July 2021

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