Australian Government
Department of Health
Therapeutic Goods Administration

CTD modules 2, 3, 4 and 5 for registered complementary medicine applications

Australian Regulatory guidelines

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TGA Health Safety Regulation

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Introduction

This document provides guidance for applicants on information required for modules 2 to 5 in dossiers for registered complementary medicines to be consistent with the Common Technical Document (CTD) format. The CTD modules 2 to 5 registered complementary medicines data requirements matrix at the end of the document provides a useful summary of the CTD module documents required for new registered complementary medicine applications.

The Mandatory requirements for an effective registered complementary medicine application describes the information, consistent with the CTD format, 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.

The General dossier requirements provides guidance for applicants to meet the general information requirements for an application for evaluation of a new registered complementary medicine.

For information required in dossiers for registered complementary medicines for CTD Module 1 refer to:

- CTD Module 1: Administrative information for registered complementary medicines - Guidance for applicants

For general information on registered complementary medicine applications refer to:

- Applications for registered complementary medicines (See steps 4, 5, and 7 for further information on the data required for different registered complementary medicine applications).
- Registered complementary and OTC medicines application and submissions: TGA Business Services (TBS) user guidance

CTD module 2: Registered complementary medicines

This guidance provides assistance in compiling Module 2 for an application to register a complementary medicine in the ARTG.

Ensuring consistency with the CTD format

Ensure you present an overall quality summary, and overviews of nonclinical and clinical safety and efficacy data, consistent with CTD Module 2.

To assist you, we have provided the general points mainly collated from the CTD guidance documents under the relevant subheadings. For a complete description of all requirements, refer to the guidelines for Module 2: Common technical document summaries.

Please note:

- There is no single CTD guidance document that explains all of the content for Module 2.

- The guidance for Modules 3, 4, and 5 each include a section on the information that must be provided in Module 2.

This guidance should be reviewed in combination with the Registered complementary medicines data requirements matrix.

Expert summaries and overviews

Include separate expert reports for:

- quality overall summary
- nonclinical overview (safety)
- clinical overview (efficacy)

For more information about what is required within each module see Common Technical Document (CTD).

Quality summary (CTD Module 2.3)

Provide a critical scientific summary explaining how you established the quality of the medicine.

When preparing your summary:

- You should normally not exceed 40 pages of text (excluding tables and figures).
- The structure of the summary should follow the scope and outline of the body of data in Module 3 and should include an introduction.
- Include sufficient information from each section to provide an overview of Module 3.
- Include discussion of key issues, integrating information for Module 3 with supporting information from other modules of the dossier (for example: qualification of impurities via toxicological studies), including cross references.
- Do not include information, data or justifications that were not already included in Module 3 or other parts of the dossier.
- Include proprietary name, non-proprietary name of the substance, company name, dosage form, strength, route of administration and proposed indications in the introduction.
- Emphasise key product parameters and justification where guidelines were not followed.
- Refer to Quality overall summary – Modules 2 and 3 for detailed guidance.

Nonclinical overview (CTD Module 2.4)

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

When preparing your nonclinical overview:

- You should normally not exceed 30 pages.

- Present the nonclinical overview in the following order: overview of nonclinical testing strategy, pharmacology, pharmacokinetics, toxicology, integrated overview and conclusions, list of literature references.
- Discuss and justify the nonclinical testing strategy.
- Interpret the nonclinical data, clinical relevance of the findings and cross-link with quality aspects and implications of the nonclinical findings for the safe use of the product.
- Consider the total amount of the active ingredient from both the medicine and other sources of the active ingredient such as food supply of the target population.
- Take into account the relevant scientific literature and properties of related products.
- Provide an appropriate justification that reviews the design of studies and any deviation from guidelines where you are using scientific literature instead of nonclinical studies.
- Discuss information of the quality of batches of drug substance used in referenced studies.
- Discuss inconsistencies in the data.
- Use consistent units throughout the overview.

Detailed guidance on the sequence and content of the nonclinical overview is described in the guidance for nonclinical summaries of Module 2 under section 2.4 Nonclinical overview.

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

Provide a critical scientific analysis of the clinical data.

When preparing your clinical overview:

- You should normally not exceed 30 pages.
- Present the clinical overview in the following order: product development rationale, overview of biopharmaceutics, overview of clinical pharmacology, overview of efficacy, overview of safety, benefits and risks conclusion, literature references.
- Include the proposed therapeutic indications, the target population, strength, dosage, duration and frequency of use, route of administration and pack size in the section on product development rationale.
- Describe the overall approach to establishing safety and efficacy of the medicine in its intended use.
- Take into consideration the history of use of the medicine and any traditional use of the medicine under subheadings in the product development rationale section.
- Present the conclusions and implications of the clinical data to create a succinct discussion and interpretation of both:
  - the clinical findings
  - any other relevant information (for example: animal data or product quality issues that may have clinical implication)
- Present strengths and limitations of the development program and study results, including important limitations, such as:

  - absence of information in some patient populations
  - use in combination with other products
- Discuss each of the following:
  - positive and negative outcomes
  - adverse events (both serious and non-serious) noting any causal relationships
- Analyse the benefits and risks of the medicine in its intended use, including interpretation of how efficacy and safety findings support the proposed dose and indication (in the form of a critical scientific assessment).
- Provide a separate explanation on how the data supports each indication and claim.
- Address particular efficacy or safety issues encountered, and how they have been evaluated and resolved.
- Explore any unresolved issues and:
  - explain why they should not be considered as barriers to approval
  - describe plans to resolve them

Further guidance on clinical overviews is provided under Section 2.5 Clinical overview of the ICH guideline on clinical efficacy.

History of use of the medicine

Provide information on the history of use of the medicine as a subsection in Module 2.5.1 (product development rationale) of the clinical overview.

Provide a summary of human exposure data, dietary, traditional and commercial use in Australia and internationally.

Provide (and categorise) the estimated number of people exposed to the medicine since the start of supply by each of the following:

- indication
- dosage and route of administration
- treatment duration
- geographical location

Traditional use

Provide information on the history of use of the medicine as a subsection in module 2.5.1 (product development rationale) of the clinical overview.

When applying evidence of traditional use, the traditionally used medicine described in this evidence and the proposed medicine must have the same traditional preparation – ensuring consistent characteristics (including dose, route of administration and duration of use).

Although long-term traditional use does not fully establish the safety and efficacy of a proposed medicine, we will consider the evidence as part of the safety evaluation.

CTD module 3: Quality information for a new registered complementary medicine

Present the data on quality in an application for evaluation of a new registered complementary medicine in a manner consistent with the European Medicines Agency (EMA) CTD module 3: ICH M4Q CTD for the registration of pharmaceuticals for human use - Quality.

Quality issues relating to the active ingredient(s) and the finished product should be addressed. A list of the scientific guidelines on quality matters that have been adopted in Australia is available on the TGA website.

You should ensure that the data address the key aspects provided in the following guidance.

Active ingredient quality information

The data required to be submitted for an active ingredient in a new registered complementary medicine is comparable to those required for an application for a new complementary medicine substance—refer to Information required in an evaluation of a substance for use as an ingredient in listed medicines.

Nomenclature of active ingredient(s)

All the components of the proposed medicine should be identified using Australian approved terminology—refer to TGA approved terminology for medicines.

Structural formula of active ingredient(s)

For simple substances and any nominated characterised constituents, provide the molecular formula, molecular weight and Chemical Abstracts Service (CAS) Registry Number or similar information that will demonstrate identity.

For complex substances, where applicable, provide a description of the constituents with known therapeutic activity or markers and other constituents.

General properties of active ingredient(s)

Provide information about the physico-chemical properties relevant to the characterisation of the substance or that may be important for the manufacture, performance or stability of its intended final dosage form, for example: solubility or particle size. Provide qualitative and quantitative particulars of the substance, including information on all physical properties such as appearance, colour, texture and smell.

Manufacturing details of active ingredient(s)

List of manufacturer(s) of active ingredient(s)

Provision of the active ingredient manufacturer's name and address, while not mandatory, will assist the TGA in the evaluation process.

Description of manufacturing process and process controls for the active ingredient(s)

A description of the manufacturing process and process controls for the active ingredient (including, for example: source and control of starting materials, reprocessing, control of critical steps and intermediates) with a flow diagram should be provided.

Where an active ingredient is derived from a herbal material, specifications for the herbal material should be provided. For control of herbal materials refer to the ICH guideline on specifications:

- Test procedures and acceptance criteria for herbal substances, herbal preparations and herbal medicinal products/ traditional herbal medicinal products EMA/CPMP/QWP/2820/00 Rev. 2

If a manufacturer is unwilling to release information required in an application to you, this information can be submitted directly to the TGA, with written authorisation from you.

Characterisation of active ingredient(s)

Identify the physical and chemical properties of the active ingredient(s).

Control of active ingredients - specifications of raw materials

Under current Australian legislation, if an ingredient is subject to a specific monograph in a default standard, it must comply with the requirements of that monograph. If there is a default standard for a finished product, the active ingredient must comply with the same default standard, for example: *British Pharmacopoeia* (BP), *United States Pharmacopoeia* (USP). If the finished product is subject to more than one monograph, the manufacturer may nominate which will be applied. In the absence of a monograph, specifications to ensure consistent quality will need to be developed.

Typically, the manufacturer of the active ingredient will develop and apply quality specifications. The finished product manufacturer is also expected to ensure that the active ingredient is of appropriate quality before including it in the manufacture of the finished product. If there are any differences between the active ingredient specifications used by the active ingredient manufacturer and the finished product manufacturer, these should be identified and discussed.

If the ingredient is herbal, the botanical species, plant part and, if an extract, the amount of the extract, the strength of the extract, extracting solvent and the equivalent amount of dried plant should be provided. Guidance on the identification of herbal materials and extracts is provided in the document titled Identification of herbal materials and extracts - Questions & answers.

Specifications of active ingredient(s)

The active ingredient acceptance specifications are a set of tests and limits that are applied to the complementary medicine substance in order to ensure that every batch is of satisfactory and consistent quality.

The development of the specifications for the active ingredient should be guided by the following scientific guidelines:

- Note for Guidance on Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances CPMP/ICH/367/96
- Guideline on specifications: Test procedures and acceptance criteria for herbal substances, herbal preparations and herbal medicinal products/ traditional herbal medicinal products EMA/CPMP/QWP/2820/00 Rev. 2

Where there is a TGA default standard for the ingredient, and if no additions have been made to the requirements of that standard, reference to the current version of the pharmacopoeia is sufficient. It is not acceptable to:

- adopt only some of the tests from a pharmacopoeial monograph
- adopt an earlier edition of the pharmacopoeial monograph or standard

In some cases, the pharmacopoeial requirements may not in themselves be sufficient to adequately control the quality and consistency of an ingredient and applicants may include additional tests.

Where non-pharmacopoeial specifications are applied, a tabulated summary of the tests, test methods and limits should be provided, together with a justification. The justification should outline how the specifications ensure that the ingredient used in a medicine formulation is of consistent quality. Specifically, identification, assay, control of impurities and other critical factors in the quality of the active ingredient should be addressed.

Impurities and incidental constituents of active ingredient(s)

For guidance refer to:

- Impurities and incidental constituents of complementary medicine substances in Information required in an evaluation of a substance for use as an ingredient in listed medicines.
- Note for Guidance on Impurities: Residual Solvents CPMP/ICH/283/95

Batch certificates of analysis for active ingredient(s)

Certificates of analysis should be provided for at least two recent commercial-scale production batches to demonstrate routine compliance with the specifications or monograph.

Certificates of analysis should also be provided for any batches of material used in toxicity tests, stability studies and clinical trials reported in support of the application. This will assist the TGA in determining whether the substance intended for supply is the same as that for which safety or stability data have been provided. If certificates of analysis are not available, justification as to why they have not been supplied must be provided.

Reference standard for active ingredient(s)

Provide information about the reference standards used in the tests, for example: identification, assay and impurities. Information should also be provided about how these reference substances were established, and where applicable, how their potencies were assigned. Where ‘in-house’ reference materials are used, provide information on how the reference material has been characterised.

Stability of active ingredients

Stability data should be provided for active ingredient(s). The data can assist in identifying any particular degradants that may be formed and should be monitored as part of the overall stability program. For guidance, refer to the scientific guideline:

- ICH Q1A (R2) Stability testing of new drug substances and drug products
- Guideline on Stability Testing: Stability Testing of Existing Active Substances and Related Finished Products CPMP/QWP/122/02 rev 1 corr

Product quality information

Description and composition of the product

Provide the medicine name and a description of the finished product that includes a visual description of the dosage form, including any special characteristics, for example: modified release.

Product development

Formulation details for the product

Include a table of all the ingredients in the product (using Australian approved name (AAN) terminology) which details:

- the purpose of each ingredient in the formulation, for example: active, disintegrant, antimicrobial preservative
- amount of each ingredient on a per unit basis
- any overages (additional amounts of ingredients, over the amounts nominated in the product's formulation, added during manufacture)
- a reference to the quality standard for each of the ingredients, for example: a pharmacopoeial monograph reference or manufacturer's specifications number

Each excipient ingredient included in a formulation must have a justifiable excipient role and be used in appropriate amounts to achieve its technical purpose.

Formulation development

Information on the development of the medicine should be provided, including a discussion of the studies that led to the proposed dosage form, formulation, method of manufacture and container.

Overages and batch to batch variation

If an overage of an active ingredient (an additional amount of an ingredient added during manufacture and greater than the amount nominated in the product's formulation) is used during manufacture, details and justification of the overage used should be included in the medicine development summary.

For some active ingredients, such as herbal substances, the weight of the active raw material used in a batch of the formulated product may vary according to the content of a standardised component. The formulation given in the application should have an annotation indicating that

the actual weight of active raw material will vary according to its estimated amount, and a formula should be provided showing how the amount of adjustment will be calculated. Validation data should be provided for the extremes of proposed ranges. Critically, where the product is a tablet or capsule, the validation data should include dissolution or disintegration data, using the test method in the proposed finished product specifications.

It is recognised that it may be necessary to vary the quantities of certain excipients from batch to batch in order to achieve acceptable results during manufacturing. Table A lists the changes to the nominal amounts of certain excipients that may be made in the manufacture of immediate release registered complementary medicines.

Table A: Allowed changes to the nominal amounts of certain excipients types

Excipient type	Range
pH adjusting ingredients	qs
Volume adjusting fluids	qs
Quantity of ingredients whose function is to contribute to viscosity	+/– 10%
Colour in tablet coating (but not in body of tablet)	qs
Solvent in granulating fluid	qs
Granulating fluid (fixed composition)	+/– 10%
Disintegrant (even if the excipient serves more than one role in the formulation)	up to +25%
Coating solution	qs*
Talc and water-soluble lubricants and glidants	–25% to +100%
Water-insoluble lubricants and glidants, except talc (for example: magnesium stearate)	+/– 25%
Filler (bulking agent) in hard gelatine capsules	+/– 10%
Polishing agents	qs
Carriers and potency-adjusting ingredients for materials of biological, herbal origin	+/– 10%
Filler (bulking agent) in tablets and soft gelatine capsules to account for the changes in the item above	+/– 10%

*Does not apply to modified release products – approval is required for any variation from the registered formulation
qs – quantum satis or 'as required'

Physiochemical and biological properties

Where a medicine has modified release characteristics or an unusual method of manufacture, the medicine development summary should include a detailed discussion of the development of those characteristics or method and any relationship with the finished product specifications. For example, for an enteric-coated tablet, dissolution and formulation studies performed during development should be discussed and related to the dissolution test in the finished product specifications.

Manufacturing process development

The selection and optimisation of the manufacturing process, particularly its critical aspects, should be explained. Where relevant, the method of sterilisation should be explained and justified.

Describe any significant changes made to the manufacturing process of the medicine used in producing scale-up, pilot and production-scale batches that may affect the composition of the substance.

Container closure system

The suitability of the container closure system used for the storage, transportation (shipping) and use of the medicine should be discussed. The discussion should consider such things as: choice of material, protection from moisture and light.

Microbiological attributes

Where appropriate, microbiological attributes of the dosage form should be discussed, including such things as the rationale for not performing microbial limits testing for non-sterile products. For sterile products, the integrity of the container closure system to prevent microbial contamination should be discussed.

Compatibility

Where applicable, the compatibility of the medicine with reconstituent diluents or dosage devices should be addressed to provide appropriate and supportive information for the labelling.

Product manufacture

Manufacturer information name(s)

All medicines must be manufactured in accordance with the principles of good manufacturing practice. The manufacturer of each step in the manufacture of the medicine that occurs in Australia must be licensed to perform that step. If a step in manufacture is carried outside Australia, then the manufacturing and control procedures used in the manufacture must be acceptable.

Australian manufacturers must comply with the PIC/S Guide to Good Manufacturing Practice for Medicinal Products.

The TGA has produced guidance for sponsors who rely on international manufacturers for any part of their production process. Refer to GMP clearance guidance.

Batch formula

A batch formula should be provided in a table format. It should include all of the components that will be used in the manufacture of the finished product and their amounts on a per batch basis (including any overages).

Description of manufacturing process and process controls

Details of the manufacturing process for the finished product should be provided for each manufacturing site. Typically, these steps may include the manufacture of the dosage form, packaging and labelling, chemical and physical testing, microbiological testing and release for supply. The manufacturing details should include a manufacturing formula and also information on:

- solvents that are used, even if they are evaporated from the medicine during manufacture
- polishing agents that do not appear in the formulation

Control of critical steps and intermediates

Tests and acceptance criteria that are applied to critical steps or intermediates in the manufacture of the finished product should be provided, such as: manufacturing acceptance criteria for a tablet granulation or in-process controls for pH during mixing of a syrup.

Process validation and/or evaluation

Description, documentation and results of the validation and/or evaluation studies should be provided for critical steps or critical assays used in the manufacturing process.

Control of excipients

Excipient ingredients subject to a specific monograph in a default standard must comply with the requirements of that monograph. If there is no relevant monograph for the ingredient, full details of the specifications for each excipient are required.

Note that there are additional restrictions and requirements for ingredients that are of animal or human origin or that are genetically modified organisms or genetically modified products.

Colours permitted in oral medicines are specified in the guidance Colourings used in medicines for topical and oral use. While topical products may include colours other than those listed in this document, the specifications for colourings used in topical products should be comparable with those permitted for oral use.

In the absence of a default standard, colours should generally conform either to the specifications in the FAO/WHO Compendium of Food Additive Specifications or to those defined in the European Commission Directive 95/45/EC.

Specifications

The specifications of excipients should be provided.

Analytical procedures

The analytical procedures used for testing the excipients should be provided, where appropriate.

Analytical validation information, including experimental data for the analytical procedures used for testing the excipients should be provided, where appropriate.

Justification of specifications

Justification for the proposed excipient specifications should be provided, where appropriate.

Excipients of human or animal origin

For excipients of human or animal origin, information should be provided regarding adventitious agents.

Novel excipients

For excipients used for the first time in a medicine or by a new route of administration, full details of manufacture, characterisation and controls, with cross references to supporting safety data (nonclinical and/or clinical) should be provided according to the medicine ingredient format.

Control of the finished product

Specifications

The finished product specifications should be provided. Refer to 'Finished product specifications' in Quality for listed medicines for guidance on the information required in a finished product specification.

The specification should include both the batch release and expiry specifications. Where the expiry specifications differ from the batch release specifications, this should be noted. The batch release limits must be chosen in order to guarantee that all batches will comply with the expiry specifications throughout the product's shelf life. The limits applied at batch release should be discussed in terms of their ability to ensure this.

The specifications should take into account any overages and the results obtained in the stability studies.

Where the product is subject to a default standard the expiry specifications must include all of the tests and limits therein. If the applicant considers that nominated test methods are unsuitable for the product, the applicant may propose other, appropriately validated, methods.

Useful guidance on the development of product specifications is provided in the following scientific guidelines:

- Specifications: Note for Guidance on Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances CPMP/ICH/367/96.

For demonstration of quality for herbal complementary medicines, the following scientific guidelines provide useful guidance:

- Quality of herbal medicinal products/ traditional herbal medicinal products EMA/CPMP/QWP/2819/00 Rev. 2
- Test procedures and acceptance criteria for herbal substances, herbal preparations and herbal medicinal products/ traditional herbal medicinal products CPMP/QWP/2820/00 Rev. 2
- Quality of combination herbal medicinal products/ traditional herbal medicinal products EMEA/HMPC/CHMP/CVMP/214869/06.

Specifications should also take into account Australian legislative requirements for finished products.

The general monographs of the BP, *European Pharmacopoeia* (Ph. Eur.) and USP are also relevant, for example: the BP monograph for oral liquids, which includes requirements for dose and uniformity of dose of oral drops and also uniformity of delivered dose from multidose containers. The most recent edition of the cited pharmacopoeia should be used.

Consent to supply the product is required (refer to Consent to supply goods that are not compliant with prescribed standards) where a finished product does not comply with Australian legislative requirements, for example: Therapeutic Goods Order No. 78 - Standard for Tablets and Capsules (TGO 78).

Analytical procedures

Details of analytical methods should be provided for all tests proposed in the specifications. Appropriately validated methods should be used.

Details of the analytical method validation should also be provided in the dossier.

Batch certificates of analysis

You must provide at least three certificates of analysis for the final product to demonstrate compliance with batch release specifications. These certificates should relate to one or more production batches of the medicine or to trial batches if production batches have not been manufactured. In such a case, you should identify any differences between the trial process and the manufacturing process and undertake to provide certificates of analysis for at least two production batches after registration has been achieved.

Residual solvents in non-pharmacopoeial products

It is necessary to consider the total amount of residual solvents that may be present in the finished product. This includes solvent residues resulting from the manufacture of the finished product. Depending on the amounts and types of solvent residues, it may be appropriate to include a test and limits for residual solvents in the finished-product specifications. Tests and limits in the specifications, or justification for not including them, should be based on the BP Appendix VIIIL – Residual Solvents.

Impurities in non-pharmacopoeial products

The specifications for finished products for which there is no default standard, should include tests and limits for impurities related to the active ingredient. For impurity limits, the results of stability studies should be taken into account and reference should be made to information on toxicity. Specifically, the amount and types of impurities that were detected in the stability studies should be consistent with the expiry specifications and the proposed shelf life. Consideration also needs to be given to the materials examined in the toxicity studies so that the product is consistent with the submitted safety data.

Where the active ingredient is a chemical entity, guidance on the amount and type of information needed on degradation products of the active ingredient can be found in the scientific guidelines:

- Note for Guidance on Impurities in New Drug Products CPMP/ICH/2738/99.
- Guideline for elemental impurities ICH Q3D(R1)

Microbiological requirements for non-sterile products

All non-sterile dosage forms should include limits for microbial content in the finished product batch release and expiry specifications. The Therapeutic Goods Order No. 100 – Therapeutic

Goods (Microbiological Standards for Medicines) Order 2018 (TGO 100) specifies the minimum microbiological requirements with which a medicine must comply throughout its shelf life.

It is not a requirement that every batch of a product (with a low risk of contamination) be tested at batch release. Once it has been demonstrated, by testing a number of routine production batches to establish a product history, that the manufacturing processes do not permit contamination by excessive numbers of microorganisms, testing may be reduced to once every 6 to 12 months or some other selected basis, for example: every tenth batch.

Products with significant water content (for example: creams, gels and oral liquids) are likely to support microbial growth. Such products should include tests and limits for microbial content in both the batch release and expiry specifications.

For products containing an antimicrobial preservative, both the batch release and expiry specifications should include physicochemical tests and limits for content of preservatives. Given that the effectiveness of many preservatives is pH dependent, the specifications for such products should usually include requirements for pH that will ensure preservative efficacy. The expiry limits for the preservative should be supported by preservative efficacy testing that is performed during stability testing.

Microbiological requirements for sterile products

The official requirements for sterility tests in Australia are those specified in the current default standards. The TGA Guidelines for sterility testing of therapeutic goods provide guidance for sterility testing of sterile therapeutic goods supplied in Australia for human use. These guidelines, however, are not mandatory for industry.

Generally, products that are required to be sterile (for example: for ophthalmic use) will require extremely stringent microbiological specifications together with detailed information on manufacturing steps that ensure sterility.

Justification of finished product specifications

The suitability of the tests, limits and test methods proposed for the finished product should be discussed with reference to relevant standards, the results of the method validation studies and the ability of the specifications to guarantee the quality and consistency of the finished product.

Reference standards or materials

Information on the reference standards or reference materials used for testing of the medicine should be provided, if not previously provided.

Container closure system

A description of the container and closure system should be provided, including the materials used. The suitability of the container should be discussed in terms of its compatibility with the medicine and also its performance in protecting the medicine physically, including from exposure to moisture and light.

In the case of 'standard' package types, it may be sufficient to simply describe the packaging. Many applicants provide diagrams of the packaging material, identifying bottle or box dimensions, and this is helpful. If the packaging material is unusual, very detailed information should be provided on its composition, as well as an assessment of the potential for undesirable material to be leached from the packaging into the medicine.

Child resistant closures

TGO No. 95 – Child-resistant packaging requirements for medicines 2017 (TGO 95) specifies requirements relating to the use of child-resistant packaging (CRP) for medicines that may present a significant risk of toxicity to children if accidentally ingested and also specifies the performance requirements that packaging must meet in order to be considered child-resistant. TGO 80 applies to medicines containing any of the ingredients specified in the First Schedule to the Order, as well as other medicines that imply, through their presentation, that the packaging is child-resistant. Presentations considered to indicate child-resistant packaging include closures with the push-down and turn graphics, typically used on child-resistant caps, and label statements referring to the closure as being child-safe or designed to prevent access by children.

Tamper-evident packaging

Tamper-evident packaging (TEP) of therapeutic goods that may be vulnerable to tampering (either deliberate or accidental) is important in ensuring consumer safety and the integrity of the goods. Where sponsors may choose to apply TEP to therapeutic products, the products should meet the requirements of the Tamper-evident packaging (TEP) code of practice. This code of practice refers to therapeutic goods that are unscheduled or in Schedule 2 or 3 to the Poisons Standard and are administered transdermally, orally or come into contact with mucous membranes.

Measuring devices

Under current Australian legislation some measuring devices or dose delivering devices may be considered as Class 1 medical devices—please refer to the Australian Regulatory Guidelines for Medical Devices (ARGMD) for further guidance.

Finished product stability

Stability summary and conclusion

The types of studies conducted, protocols used and the results of the studies should be summarised. The summary should include, for example: conclusions with respect to shelf life and, if applicable, in-use storage conditions and shelf-life.

Stability data

The stability data must be sufficient to demonstrate, or indicate with a high probability, that the medicine intended for market will remain safe, of consistent quality and efficacious throughout its shelf life. The stability data will form the basis for setting a shelf life and recommended storage conditions. Refer to the scientific guideline:

- ICH Q1A (R2) Stability testing of new drug substances and drug products
- Guideline on Stability Testing: Stability Testing of Existing Active Substances and Related Finished Products CPMP/QWP/122/02 rev 1 corr.

Post-registration requirements

Sponsors of therapeutic goods are required to carry out an ongoing stability testing program on each product (refer to the PIC/S Guide for Good Manufacturing Practice for Medicinal Products).

Where a shelf life has been allocated on the basis of:

- accelerated testing

- data generated on a related formulation
- data generated on the same formulation in a different container; or
- data generated on batches other than production batches

It is a requirement to provide an assurance that full stability testing will begin on at least the first two production batches and continue for the full period of the product's shelf life (at the recommended storage condition) and that any adverse trends will be reported to the TGA.

Data may be requested for review at any time or followed up by the TGA's inspectors during GMP inspections of the manufacturing site. If it is found that the required testing has not been carried out or that adverse trends have not been reported to the TGA, appropriate action may be taken, which may include cancellation of the medicine's registration.

Stability protocol for self-assessable shelf life extension

A medicine's shelf life may be extended on the basis of stability testing conducted according to a protocol specifically approved for this purpose. For a stability protocol to be considered for the purpose of self-assessable shelf life extensions, it is normally necessary for at least twelve months of data, generated at the maximum recommended storage temperature, to be available on at least two production batches of the proposed formulation, in the container proposed for marketing or one that is less protective.

To provide a suitable margin of safety, the limits for results of critical test parameters should normally be a little tighter than the expiry limits. Where some results are outside these limits, the sponsor may submit the data for evaluation by the TGA.

The protocol should be a stand-alone document, which includes:

- a statement of the intended purpose (for example: 'This protocol is intended for notification of shelf life increases of up to x years following self-assessment of stability data'), or a statement of the criteria for notifying a shelf-life increase (for example: 'Full-term stability data will be generated using two production batches stored at x°C. All analytical results obtained will comply with the protocol acceptance criteria; otherwise, the TGA will be notified immediately')
- the precise formulation of the medicine (if overages are included, this should be stated and a justification provided)
- the immediate container specifications
- the storage conditions to be included on the label
- the finished product expiry specifications and the protocol acceptance criteria (including acceptable limits for results of each test)
- a statement of the proposed tests and validated test methods (validation data should be included if it has not already been supplied to the TGA)
- a matrix indicating the time stations at which each of the tests will be conducted as well as the storage conditions to be used in the study

Shelf life extensions according to an approved protocol

Provided that a protocol for self-assessable shelf life extensions has been approved by the TGA for a particular product, the shelf life extension for that medicine may be implemented following notification to the TGA, provided that:

- all results up to the end of the notified shelf life fall within the acceptance criteria as specified in the approved stability protocol
- no other changes to the information previously provided to the TGA about this medicine (other than as specified in the notification) have been made, or are currently proposed to be made
- a stability testing protocol has been approved and a copy of the approval letter is attached to the notification
- at least two full production batches of the Australian formulation packed in the approved container have been used in the studies
- the shelf life is not longer than the time for which stability data meeting the approved protocol are available, and in any case is not longer than five years

Prospective extensions of shelf life for individual batches

Under certain circumstances, the TGA may approve a limited extension of shelf life for individual batches approaching their expiry date in the absence of the stability data. The prerequisites are as follows:

- the existing shelf life should be at least two years
- stability data should be available to the TGA, which validate the existing shelf life
- a recent (less than two months old), dated certificate of analysis should be supplied for the batch, showing compliance with specifications, together with the results obtained at batch release
- the sponsor should provide an assurance that it has commenced or intends to commence a stability study to validate a permanent extension of the shelf life, unless it is intended as a purely one-off event to ensure continued supply

Prospective extensions of more than six months, or to a shelf life of more than five years, are not normally acceptable.

Data requirements for generic registered complementary medicines

Quality data is required in support of generic complementary medicines to ensure:

- consistency and quality of the manufacturing process for the medicine
- the quality of the ingredients and the final product
- the combination of ingredients used to make the final product

CTD module 4 Nonclinical data for a new registered complementary medicine

If an ingredient or medicine is well described and appropriately referenced in reputable texts or publications (for example: Martindale-The Complete Drug Reference) the TGA will consider these sources in the assessment of safety and efficacy where these are provided in the application. Indications, dosage and route of administration must be consistent with the reference provided. For guidance for applicants choosing to submit a literature-based submission, see Literature-based submissions for listed medicines and registered complementary medicines.

For other new medicines that are not well described in literature, nonclinical and clinical data will be required to support the safety and efficacy of the medicine. Safety and efficacy data should be presented as 'nonclinical' and 'clinical' data modules (consistent with the CTD Modules 4 and 5).

Data that demonstrate the safety of the medicine include information on history and pattern of use, biological activity, toxicology, clinical data and reports of adverse reactions. The overall safety of the medicine is dependent upon its formulation, its intended therapeutic purpose, dosage, method or route of administration, duration of use, the target patient group (such as children or the elderly) and the potential for interaction with other medicine(s).

Safety may be established by detailed reference to the published literature and/or the submission of original study data. Where there is sufficient evidence based on human experience to support safety, the absence of extensive nonclinical investigations may be justifiable. Note that anecdotal or limited clinical reports of efficacy alone are not considered evidence of efficacy and safety.

Safety data is usually not required when:

- each ingredient is specified in Therapeutic Goods (Permissible Ingredients) Determination and its use complies with the requirements
- the quality of the active ingredient(s) complies with relevant default standards or compositional guidelines
- no new safety data is available beyond what was considered to establish safety for listed medicines.

In most cases, you do not need to provide safety data in support of generic complementary medicines.

Pharmacology

Primary pharmacodynamics: *in vitro* and *in vivo*

Studies on primary pharmacodynamics should be provided and evaluated.

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

Studies on secondary pharmacodynamics should be provided by organ system, where appropriate, and evaluated.

Safety pharmacology

Safety pharmacology studies should be provided and evaluated. In some cases, secondary pharmacodynamic studies can contribute to the safety evaluation when they assess potential adverse effects in humans.

Pharmacodynamic drug interactions

Where they have been performed, pharmacodynamic drug interactions should be provided.

Pharmacokinetics

Analytical methods and validation reports

Provide the methods of analysis for biological samples, including the detection and quantification limits of analytical procedures.

Absorption

Provide data on the extent and rate of absorption (*in vivo* and *in vitro* studies) and kinetic parameters, bioequivalence and/or bioavailability.

Distribution

Where available, provide data tissue distribution studies, protein binding and distribution in blood cells and placental transfer studies.

Metabolism

Where available, provide data on:

- chemical structures and quantities of metabolites in biological samples
- possible metabolic pathways
- pre-systemic metabolism
- *in vitro* metabolism including P450 studies
- enzyme induction and inhibition

Excretion

Where available provide data on routes and extent of excretion and excretion in breast milk.

Pharmacokinetic drug interactions (nonclinical)

If they have been performed, provide nonclinical pharmacokinetic drug interaction studies (*in vitro* and *in vivo*).

Provide details of any contraindications or interactions with conventional and non-conventional medicines.

Other pharmacokinetic studies

If studies have been performed in nonclinical models of disease they should be provided and evaluated.

Toxicology

Single dose toxicity

The single dose data should be provided in order of species, by route and evaluated.

Repeat dose toxicity

Studies should be provided in order of species, by route and by duration and evaluated.

Genotoxicity: *in vitro* and *in vivo*

Where available, *in vitro* and *in vivo* mammalian and non-mammalian cell system genotoxicity studies should be provided and evaluated**.**

Carcinogenicity: long term studies and short or medium term studies

Where available, carcinogenicity studies should be provided and evaluated.

Reproductive, developmental toxicity

Where available, provide and evaluate studies on:

- fertility and early embryonic development
- embryo-fetal development
- prenatal and postnatal development
- studies in offspring.

Local tolerance

If local tolerance studies have been performed, these should be provided and evaluated.

Other toxicity studies

Provide any other studies such as: antigenicity, immunotoxicity, mechanistic studies, dependence, metabolites and impurities.

CTD module 5: Clinical data

Clinical data should preferably be presented as specified in Modules 2.5 Clinical Overview, 2.7 Clinical Summary and Module 5 Clinical Study Reports of the CTD format. The clinical overview provides a critical analysis of the clinical data in the dossier while the clinical summary provides a detailed, factual summary of the clinical information.

Pharmacology studies

Pharmacokinetics

Include data on the action of the body on the medicine including absorption, distribution, metabolism and elimination of the medicine. Include information on possible pharmacokinetic interactions with other agents for example: alcohol, grapefruit juice, other medicines.

Pharmacodynamics

Include information on the mechanism of action, if known. Include information to justify the proposed dose and dose interval and any information that may be relevant to formulation differences in the submitted studies and to possible pharmacodynamic interactions with other medicines.

Efficacy studies

Controlled and uncontrolled efficacy clinical trials

Provide and evaluate any published and unpublished efficacy clinical trials.

Australian Clinical Trials provides information for sponsors developing clinical trials for a medicine or a new complementary medicine substance.

Efficacy-related PI/CMI comments (where applicable)

Where the medicine has a PI or CMI document, provide evidence or a justification that support the proposed efficacy related statements in the relevant sections of the PI. This can be provided in a marked up copy of the PI or CMI.

Data requirements for generic registered complementary medicines

For a generic medicine, in most cases you need to provide efficacy data (bioequivalence or therapeutic equivalence data) to demonstrate bioequivalence with the originator medicine.

Applications for new generic complementary medicines can be one of two application categories:

- RCM 3: generic complementary medicines for which you can provide an appropriate scientific justification for not providing bioequivalence data
- RCM 4: generic complementary medicines when bioequivalence studies are necessary

When bioequivalence data is required

Bioequivalence data is required:

- for all generic modified release dose forms (excluding enteric-coated tablets or capsules)
- if there is reason to believe that the bioavailability of the proposed medicine may differ from the originator medicine, which may adversely impact on efficacy and/or safety of the medicine. For example, if the medicine contains excipient(s) or has novel properties that could significantly affect gastric passage, absorption, *in vivo* solubility or *in vivo* stability of the active substance

Requirements for bioequivalence data

Include biopharmaceutic study reports in Module 5.3.1 and complete the Summary of a Bioavailability or Bioequivalence Study form for each study and include in Module 1.9.1 of the dossier.

When bioequivalence data is not required

There may be cases where a justification for not providing bioequivalence data is appropriate. These should be discussed at a pre-submission meeting. In your justification:

- include an explanation as to why the requirement is not being met
- detail the proposed alternative approach and a scientific justification for why the proposed approach is valid (with reference to any supporting documents)

Include your justifications for not providing bioequivalence data in Module 1.9.2 of the dossier.

Refer to Biopharmaceutic studies guidance, section 15.9 for more information on what to include in the justification.

Related guidance

- Biopharmaceutic studies
- Guideline on the investigation of bioequivalence CPMP/EWP/QWP/1401/98 Rev.1/corr
- Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms EMA/CHMP/EWP/280/96 –section 6, abridged application for modified release forms refer to a marketed modified release form
- CTD Module 5: Efficacy (clinical study reports) - sections 2.7.1 and 5.3.1 provide information on bioequivalence

Safety studies

Safety data is usually not required when:

- each ingredient is specified in Therapeutic Goods (Permissible Ingredients) Determination and its use complies with the requirements
- the quality of the active ingredient(s) complies with relevant default standards or compositional guidelines
- no new safety data is available beyond what was considered to establish safety for listed medicines

In most cases you do not need to provide safety data in support of generic complementary medicines.

Controlled and uncontrolled safety clinical trials

Provide and evaluate any published and unpublished safety clinical trials.

Safety-related PI/CMI comments (where applicable)

Where the medicine has a PI or CMI document, provide evidence or a justification that support the proposed safety related statements in the relevant sections of the PI. This can be provided in a marked up copy of the PI or CMI.

Post-marketing data

The application should include all relevant post-market data, including published and unpublished data. Any safety issues identified following marketing should be highlighted and any regulatory action relating to safety taken by an international regulatory agency should be detailed. The data should be presented as a tabulation of the adverse events that have been reported, including any serious adverse events and any potentially serious interactions with other medicines.

A Periodic Safety Update Report (PSUR) is acceptable as post-marketing data.

CTD module 2 to 5 data requirements matrix for new registered complementary medicine applications

The registered complementary medicines data requirements matrix (the 'matrix') (tables 2 to 5) provides a useful summary of the CTD module documents required for new registered complementary medicines. For more detailed information on data requirements for each RCM application category refer to the Mandatory requirements for an effective registered complementary medicine application.

How to use the matrix

Determine the appropriate application category in the Applications for registered complementary medicines and use the matrix to obtain an indication of which documents you need to provide. The information included in CTD Module 1 guidance will also provide assistance in determining what documents are required. For full folder names, refer to The Common Technical Document.

The codes in the matrix are provided in Table 1.

Table 1: Description of codes used in data matrix

Code	Description
R (red)	The document(s) and/or appropriate scientific justification for not providing document(s) are required for a valid application.
D (green)	The document(s) are dependent on the kind of application in a particular category for the particular dossier.
O (blue)	The document(s) are optional. There is no requirement for the document(s) to be submitted with the application. However, the document(s) can be provided if the applicant considers the information is relevant to the application.
Blank:	The document(s) are not relevant and should not be submitted.

Table 2: CTD module 2 data requirements matrix for new registered complementary medicines

Module	Name	RCM 1	RCM 2	RCM 3	RCM 4	RCM 5	File or folder name
2	**CTD Summaries**						m2
2.2	**CTD introduction**			O	O	O	22-intro
2.3	**Quality overall summary**				D	R	23-qos
2.4	**Nonclinical overview**				D	R	24-nonclin-over

Module	Name	RCM 1	RCM 2	RCM 3	RCM 4	RCM 5	File or folder name
2.5	**Clinical overview**				D	R	25-clin-over
2.6	**Nonclinical written and tabulated summaries**				O	O	26-nonclin-sum
2.7	**Clinical summary**				O	O	27-clin-sum

Table 3: CTD module 3 data requirements matrix for new registered complementary medicines

Module	Name	RCM 1	RCM 2	RCM 3	RCM 4	RCM 5	File or folder name
3	**Quality**			R	D	R	m3
3.2.S	**Drug substance**						32s-drug-sub
3.2.S.1	**General Information**						32s1-gen-info
3.2.S.1.1	Nomenclature			R	D	R	nomenclature
3.2.S.1.2	Structure			R	D	R	structure
3.2.S.1.3	General Properties			R	D	R	general-properties
3.2.S.2	**Manufacture**						32s2-manuf
3.2.S.2.1	Manufacturer(s)			O	D	D	manufacturer
3.2.S.2.2	Description of manufacturing process and process controls			O	D	D	manuf-process-and-controls
3.2.S.2.3	Control of materials			O	D	D	control-of-materials
3.2.S.3	**Characterisation**			R	D	R	32s3-charac
3.2.S.3.1	Elucidation of structure and other characteristics			R	D	R	elucidation-of-structure
3.2.S.3.2	Impurities			R	D	R	impurities

Module	Name	RCM 1	RCM 2	RCM 3	RCM 4	RCM 5	File or folder name
3.2.S.4	**Control of Drug Substance**			R	D	R	32s4-contr-drug-sub
3.2.S.4.1	Specification			R	D	R	32s41-spec
3.2.S.4.2	Analytical Procedures			R	D	R	32s42-analyt-proc
3.2.S.4.3	Validation of analytical procedures			R	D	R	32s43-val-analyt-proc
3.2.S.4.4	Batch analyses			R	D	R	32s44-batch-analys
3.2.S.4.5	Justification of Specification			R	D	R	32s45-justif-spec
3.2.S.5	**Reference standards or materials**			R	D	R	32s5-ref-stand
3.2.S.6	**Container closure system**			R	D	R	32s6-cont-closure-sys
3.2.S.7	**Stability**			R	D	R	32s7-stab
3.2.S.7.1	Stability summary and conclusions			R	D	R	stability-summary
3.2.S.7.3	Stability data			R	D	R	stability-data
3.2.P	**Drug product**			R	D	R	32p-drug-prod
3.2.P.1	**Description and composition of the drug product**			R	D	R	32p1-desc-comp
3.2.P.2	**Pharmaceutical development**			R	D	R	32p2-pharm-dev
3.2.P.2.1	Components of the drug product			R	D	R	
3.2.P.2.1.1	Drug Substance			R	D	R	

Module	Name	RCM 1	RCM 2	RCM 3	RCM 4	RCM 5	File or folder name
3.2.P.2.1.2	Choice of the excipients listed in 3.2.P.1			R	D	R	
3.2.P.2.2	Drug Product			R	D	R	
3.2.P.2.2.1	Formulation development			R	D	R	
3.2.P.2.2.2	Overages			R	D	R	
3.2.P.2.2.3	Physicochemical and biological properties			R	D	R	
3.2.P.2.3	Manufacturing process development			R	D	R	
3.2.P.2.4	Container Closure System			R	D	R	
3.2.P.2.5	Microbiological attributes			R	D	R	
3.2.P.2.6	Compatibility			R	D	R	
3.2.P.3	**Manufacture**			R	D	R	32p3-manuf
3.2.P.3.1	Manufacturer(s)			R	D	R	manufacturers
3.2.P.3.2	Batch formula			R	D	R	batch-formula
3.2.P.3.3	Description of manufacturing process and process controls			R	D	R	manuf-process-and-controls
3.2.P.3.4	Controls of critical steps and intermediates			R	D	R	control-critical-steps
3.2.P.3.5	Process validation and/or evaluation			R	D	R	process-validation
3.2.P.4	**Control of excipients**	D		R	D	R	32p4-contr-excip

Module	Name	RCM 1	RCM 2	RCM 3	RCM 4	RCM 5	File or folder name
3.2.P.4.1	Specifications	D		R	D	R	specifications
3.2.P.4.2	Analytical procedures	D		R	D	R	analytical-procedures
3.2.P.4.3	Validation of analytical procedures	D		R	D	R	validation-analyt-procedures
3.2.P.4.4	Justification of specifications	D		R	D	R	justification-of-specifications
3.2.P.4.5	Excipients of human or animal origin	D		R	D	R	excipients-human-animal
3.2.P.4.6	Novel excipients	D		R	D	R	novel-excipients
3.2.P.5	**Control of drug product**			R	D	R	32p5-contr-drug-prod
3.2.P.5.1	Specification(s)		D	R	D	R	32p51-spec
3.2.P.5.2	Analytical procedures			R	D	R	32p52-analyt-proc
3.2.P.5.3	Validation of analytical procedures			R	D	R	32p53-val-analyt-proc
3.2.P.5.4	Batch analyses		D	R	D	R	32p54-batch-analys
3.2.P.5.5	Characterisation of impurities			R	D	R	32p55-charac-imp
3.2.P.5.6	Justification of specifications			R	D	R	32p56-justif-spec
3.2.P.6	**Reference standards or materials**			R	D	R	32p6-ref-stand
3.2.P.7	**Container closure system**		D	R	D	R	32p7-cont-closure-sys
3.2.P.8	**Stability**			R	D	R	32p8-stab

Module	Name	RCM 1	RCM 2	RCM 3	RCM 4	RCM 5	File or folder name
3.2.P.8.1	Stability summary and conclusion			R	D	R	stability-summary
3.2.P.8.3	Stability data			R	D	R	stability-data

Table 4: CTD module 4 data requirements matrix for new registered complementary medicines

Module	Name	RCM 1	RCM 2	RCM 3	RCM 4	RCM 5	File or folder name
4	**Nonclinical study reports**						m4
4.1	**Table of contents**	O	O	O	O	O	41-toc
4.2	**Study reports**				D	R	42-stud-rep
4.2.1	**Pharmacology**				D	R	421-pharmacol
4.2.1.1	Primary pharmacodynamics				D	R	4211-prim-pd
4.2.1.2	Secondary pharmacodynamics				D	R	4212-sec-pd
4.2.1.3	Safety pharmacology				D	R	4213-safety-pharmacol
4.2.1.4	Pharmacodynamic drug interactions				D	R	4214-pd-drug-interact
4.2.2	**Pharmacokinetics**				D	R	422-pk
4.2.2.1	Analytical methods and validation reports				D	R	4221-analyt-met-val
4.2.2.2	Absorption				D	R	4222-absorp
4.2.2.3	Distribution				D	R	4223-distrib
4.2.2.4	Metabolism				D	R	4224-metab
4.2.2.5	Excretion				D	R	4225-excr

Module	Name	RCM 1	RCM 2	RCM 3	RCM 4	RCM 5	File or folder name
4.2.2.6	Pharmacokinetic drug interactions				D	R	4226-pk-drug-interact
4.2.2.7	Other pharmacokinetic studies				D	R	4227-other-pk-stud
4.2.3	**Toxicology**				D	R	423-tox
4.2.3.1	Single-dose toxicity				D	R	4231-acute-tox
4.2.3.2	Repeat-dose toxicity				D	R	4232-repeat-dose-tox
4.2.3.3	**Genotoxicity**				D	R	4233-genotox
4.2.3.3.1	In vitro				D	R	42331-in-vitro
4.2.3.3.2	In vivo				D	R	42332-in-vivo
4.2.3.4	**Carcinogenicity**				D	R	4.2.3.4
4.2.3.4.1	Long-term studies				D	R	42341-lt-stud
4.2.3.4.2	Short- or medium-term studies				D	R	42342-smt-stud
4.2.3.5	**Reproductive and developmental toxicity**				D	R	4235-repro-dev-tox
4.2.3.5.1	Fertility and early embryonic development				D	R	42351-fert-embryo-dev
4.2.3.5.2	Embryo-fetal development				D	R	42352-embryo-fetal-dev
4.2.3.5.3	Prenatal and postnatal development, including maternal function				D	R	42353-pre-postnatal-dev
4.2.3.5.4	Studies in which the offspring (juvenile animals) are dosed and /or further evaluated				D	R	42354-juv

Module	Name	RCM 1	RCM 2	RCM 3	RCM 4	RCM 5	File or folder name
4.2.3.6	**Local tolerance**				D	R	4236-loc-tol
4.2.3.7	**Other toxicity studies**				D	R	4237-other-tox-stud
4.2.3.7.1	Antigenicity				D	R	42371-antigen
4.2.3.7.2	Immunotoxicity				D	R	42372-immunotox
4.2.3.7.3	Mechanistic studies				D	R	42373-mechan-stud
4.2.3.7.4	Dependence				D	R	42374-dep
4.2.3.7.5	Metabolites				D	R	42375-metab
4.2.3.7.6	Impurities				D	R	42376-imp
4.3	**Literature references**				D	R	43-lit-ref

Table 5: CTD module 5 data requirements matrix for new registered complementary medicines

Module	Name	RCM 1	RCM 2	RCM 3	RCM 4	RCM 5	File or folder name
5	**Clinical study reports**						m5
5.1	**Table of contents**				O	O	51-toc
5.2	**Tabular listing of all clinical studies**				D	R	52-tab-list
5.3	**Clinical study reports**				D	R	53-clin-stud-rep
5.3.1	Reports of biopharmaceutic studies				D	R	531-rep-biopharm-stud
5.3.2	Reports of studies pertinent to pharmacokinetics using human biomaterials				D	R	532-rep-stud-pk-human-biomat
5.3.3	Reports of human pharmacokinetic (PK) studies				D	R	533-rep-human-pk-stud

Module	Name	RCM 1	RCM 2	RCM 3	RCM 4	RCM 5	File or folder name
5.3.4	Reports of human pharmacodynamic (PD) studies				D	R	534-rep-human-pd-stud
5.3.5	**Reports of efficacy and safety studies**				D	R	535-rep-effic-safety-stud
5.3.5.1	Study reports of controlled clinical studies pertinent to the claimed indication				D	R	5351-stud-rep-contr
5.3.5.2	Study reports of uncontrolled clinical studies				D	R	5352-stud-rep-uncontr
5.3.5.3	Reports of analyses of data from more than one study				D	R	5353-rep-analys-data-more-one-stud
5.3.5.4	Other study reports				D	R	5354-other-stud-rep
5.3.6	Reports of post-marketing experience				D	D	536-postmark-exp
5.4	**Literature references**				D	R	54-lit-ref

Version history

Version	Description of change	Author	Effective date
V1.0	Information for original publication extracted from pages 156 to 201 of ARGCM V8.0. New introductory paragraph. Data matrix moved to back of document. Information under clinical pharmacokinetics and pharmacodynamics revised and corrected. Headings changed in matrix to be consistent with ICH M4Q, M4S and M4E documents. Table numbers changed in matrix. Requirements for 3.2.S.2 corrected for RCM 5 from 'O' to 'D'. Requirements for 3.2.P.5.1, 3.2.P.5.4 and 3.2.P.7 corrected to 'D' for RCM 2 to align with the Mandatory requirements for an effective registered medicines application. Guidance related to generic medicines and medicines only containing ingredients permitted for listed medicines has been moved to the relevant modules.	Complementary & OTC Medicines Branch	May 2020

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