Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian regulatory guidelines for complementary medicines

Part D: Registered complementary medicines

June 2013

Draft for consultation

TGA Health Safety Regulation

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About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <http://www.tga.gov.au>.

GENERAL COMMENTS:

1. This is an important avenue and ASMI remain committed to work with TGA to improve the regulatory system
2. Overall we perceive this draft guideline to be written for the highest risk non-prescription complementary medicines. It provides no advice for lower risk applications (nor for prescription applications) or when to consider what details may be necessary. The range of risks requires a range of approaches, consistent with risk-based regulation. Registered CMs pose a similar or lower risk profile to that of registered OTCs. We note that pre-OTC BPR, guidance was written to clarify under what circumstances different levels of safety & efficacy data would be required. Throughout this draft we have copied and pasted relevant sections of the current ARGOM to illustrate a consistent approach.
3. It is not helpful to provide an incomplete guideline for review and consultation. 13 of 18 important attachments are omitted as they are under review by TGA. Not even their titles have been provided for reference. This means the document is to be considered in isolation from what may be important and relevant material. Could Part D not have been held back and issued once the attachments had been prepared/finalised/ready for consultation?
4. The document contains a great deal of repetition. This is counter-productive in terms of clarity. May we suggest the concise overview followed by the tables, then each table of requirements immediately followed by its specific detail; in chronological order?
5. On Page 12 the original draft guideline specifies: *"Although the CTD format is not a mandatory requirement for a new registered complementary medicine application, presentation in this manner will expedite evaluation. However, for some complementary medicine registration applications, not all parts of the CTD modules will be relevant. Where data are not available for a particular CTD heading, a justification* ***must*** *be provided."* It should **not** be necessary to provide a justification for every non-applicable section; rather, justification should be required only where data would normally be provided. See *Guidelines for electronic OTC dossiers V 1.0 April 2013,* p7. We refer also to the tables indicating whether CTD modules are mandatory, dependent on the type of application, optional, or not applicable in the *OTC dossier documents matrix*, V.1.0, April 2013, pp 5-12.
6. There is no discussion of requests by the evaluators for further information and how these will be managed. Sponsors would prefer to receive all questions at the one time so that responses can be prepared and submitted with confidence. Currently we hear reports of

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sponsors r eceiving series of ques tions ov er time, and t his can seriously extend the evaluation period.

7. There are no target timeframes.

8. There is no provision for clones.

9. There is no discussion of standard reference text (monograph)– based submissions.

There is no consideration of risk-based treatment of products. There is considerable difference bet ween a m ultivitamin-mineral s upplement which i s r egistrable onl y due t o a high-level i ndication, and a medicine c ontaining a ne w nutrient d erivative without a documented hi story of us e. Similarly, t here i s a gr eat di fference bet ween a nut ritional supplement with one o r two scheduled ingredients, and a p roduct c ontaining a highly purified herbal e xtract produced w ith a completely new technology. We would appreciate the opportunity to discuss how risk based categorisation of applications for complementary medicines might be approached.

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Confidentiality
All submissions received will be placed on the TGA's Internet site, unless marked confidential. Any confidential material contained within your submission should be provided under a separate cover and clearly marked "IN CONFIDENCE". Reasons for a claim to confidentiality must be included in the space provided on the TGA submission coversheet. For submission made by individuals, all personal details, other than your name, will be removed from your submission before it is published on the TGA's Internet site. In addition, a list of parties making submissions will be published. If you do not wish to be identified with your submission you must specifically request this in the space provided on the submission coversheet.

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ARGCM Part D: Registered complementary medicines

Overview of registered complementary medicines

While the majority of complementary medicines are eligible for listing on the Australian Register of Therapeutic Goods (ARTG), some are not, such as medicines that:

- contain an ingredient that is not permitted for use in listed medicines [see Schedule 4, Part 4, Division 1 of the Therapeutic Goods Regulations 1990 (the Regulations)]; or
- contain an ingredient or ingredient component that is subject to the conditions of a Schedule (or relevant appendix) to the Standard for the Uniform Scheduling of Medicines and Poisons (the Poisons Standard); or
- are required to be sterile; or
- have therapeutic indications that are not permitted for listed medicines.

The above types of medicines are required to be registered on the ARTG. Registered medicines are considered to be of higher risk than listed medicines based on their ingredients and/or therapeutic indications they carry. Prior to being approved for entry on the ARTG, registered medicines are subject to critical assessment by the TGA to determine whether the proposed medicine meets the requirements for quality, safety and efficacy.

An applicant seeking registration of a complementary medicine should submit an application in accordance with Section 23 of the *Therapeutic Goods Act 1989* (the Act) (refer to 'Process for application for evaluation of a new registered complementary medicine' below).

In determining if a medicine can be approved for registration, consideration is given to: whether the quality, safety and efficacy of the medicine for the purposes for which it is to be used have been satisfactorily established; the presentation of the medicine is acceptable; and the medicine complies with all applicable legislative requirements (under section 25 of the Act).

Scheduling of registered complementary medicines

Registered complementary medicines may be subject to the conditions of a schedule to or an appendix of the Poisons Standard, for example:

- Schedule 2 – 'Pharmacy Medicine'; or
- Schedule 3 – 'Pharmacist Only Medicine'.
- Schedule 4 – 'Prescription Only Medicine'
- Schedule 8 – 'Controlled Drug'

It is important that possible scheduling requirements are considered before an application for registration is submitted - refer to the Principles of Scheduling in the Poisons Standard

[redacted] What is unclear here is the scope of the ARGCM Part D. Reading between the lines in the later detail, it appears that this guideline is only intended to apply to Non- prescription complementary medicines.
There is avoidance of any mention of S4, S8 and sterile medicines in the detail after page 7. And fees are aligned only to Non Rx applications.

What Australian regulatory guideline will apply to the evaluation of a prescription complementary medicine?

Greater clarity is required.

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and the National Coordinating Committee on Therapeutic Goods (NCCTG) Scheduling policy framework for medicines and chemicals. Medicines are not scheduled solely on the basis of toxicity. As stated in the Poisons Standard:

Although toxicity is one of the factors considered, and is itself a complex of factors, the decision to include a substance in a particular Schedule also takes into account many other criteria such as the purpose of use, potential for abuse, safety in use and the need for the substance.

Products with similar substances and indications are likely to be subject to similar schedules. If a medicine contains a substance that requires scheduling control and it is not already scheduled, the TGA may classify the substance in one of the Poisons Standard's schedules when making the registration decision. If applicants are unsure of potential scheduling of their proposed medicine they should seek advice from the TGA.

Process for application for evaluation of a new registered complementary medicine

For the purposes of this document, the term 'applicant' refers to the person who submits an application (for evaluation of a new registered complementary medicine). The applicant may or may not become the sponsor of the medicine (if the medicine is approved for registration on the ARTG). The definition of a sponsor, provided in the Act states:

> 'sponsor, in relation to therapeutic goods, means:
> (a) a person who exports, or arranges the exportation of, the goods from Australia; or
> (b) a person who imports, or arranges the importation of, the goods into Australia; or
> (c) a person who, in Australia, manufactures the goods, or arranges for another person to manufacture the goods, for supply (whether in Australia or elsewhere);
> but does not include a person who:
> (d) exports, imports or manufactures the goods; or
> (e) arranges the exportation, importation or manufacture of the goods;
> on behalf of another person who, at the time of the exportation, importation, manufacture or arrangements, is a resident of, or is carrying on business in, Australia'.

There is currently no statutory time frame for the evaluation of a new registered complementary medicine. The complexity of the medicine and its ingredients, as well as the completeness and the quality of the data submitted in the dossier will influence the length of time required for evaluation.

Route of evaluation

Legislative provisions determine the 'route of evaluation' for an application. This in turn determines data requirements, fees and the timelines. Schedule 10 of the Regulations prescribes which office within the TGA conducts the evaluation of specific therapeutic goods. Part 2 of Schedule 10 relates to complementary medicines that do not contain substances in Schedule 4, 8 and 9 of the Poisons Standard.

If an applicant is of the view that their application has been incorrectly referred to a particular TGA office for evaluation, they may make a submission to the TGA in support of

which route of evaluation they consider more appropriate. In making such a submission, the applicant should provide the TGA with all relevant information that would enable the assessment of the therapeutic good against Schedule 10 of the Regulations.

Application phases for a new registered complementary medicine

An application for a new registered complementary medicine passes through the following phases:

- **PHASE 1**: Pre-submission meeting (recommended).
- **PHASE 2**: Lodgement of application and payment of application fee.
- **PHASE 3**: Screen of application and payment of evaluation fee.
- **PHASE 4**: Evaluation of quality, safety and efficacy data, and where required, consideration by a TGA advisory committee.
- **PHASE 5**: Delegate decision.
- **PHASE 6**: Implementation.

Figure 1 illustrates the application phases for a new registered complementary medicine.

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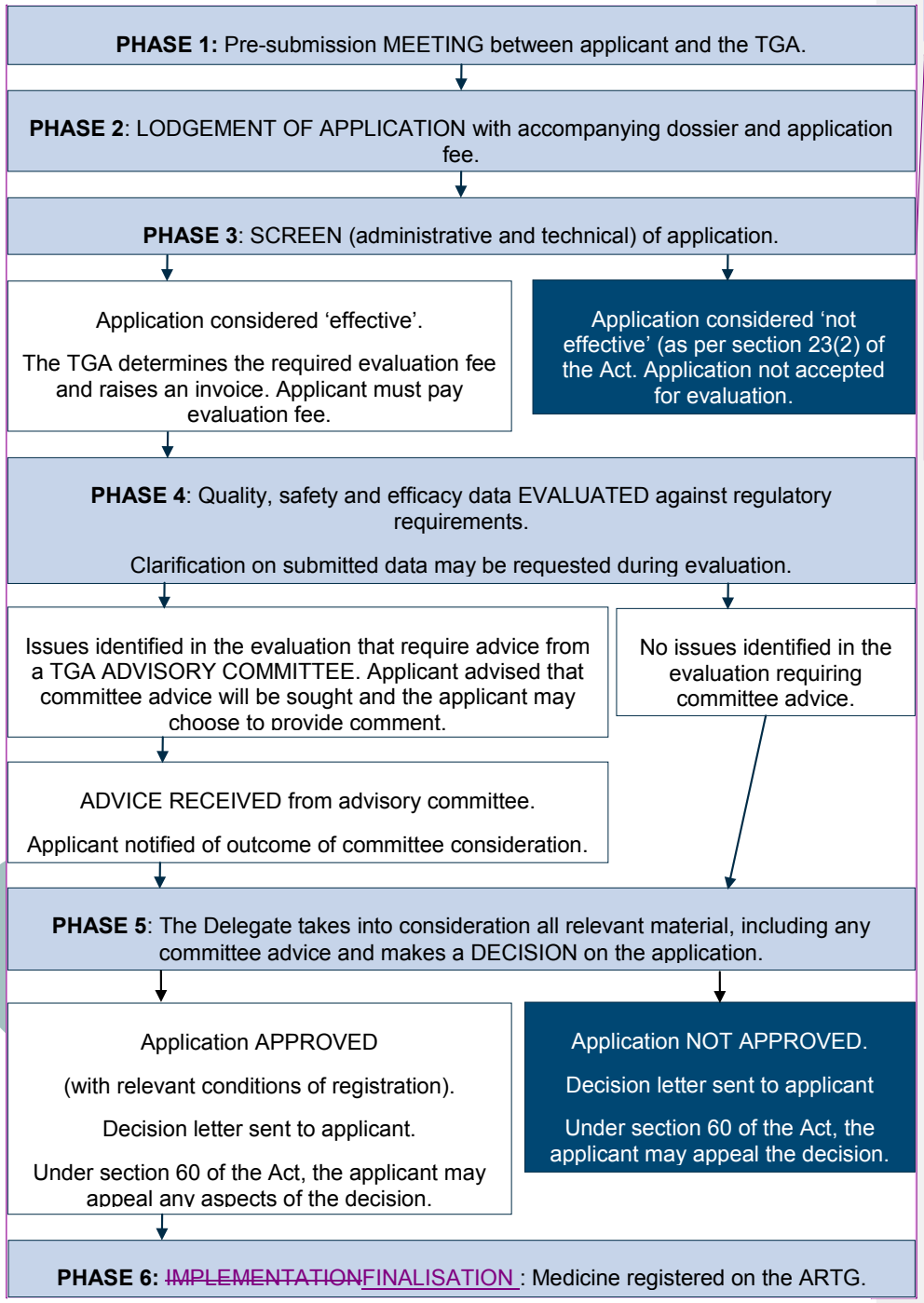
Figure 1: New registered complementary medicine application process flow chart



[redacted] In the screening process will there be an allowance for administrative errors, with e.g. a week to given to correct them?

[redacted] I find this format of flow chart somewhat difficult to navigate. It can appear that once you start tracking down the RHS text boxes your application will not be approved. Which is not the case. We prefer the Diamond decision flowchart symbol. While these are tight for space , by moving the text outside the flowchart symbols it might be achieved.

At Phase 4 – it would assist sponsors to receive one single detailed list of specific areas where the evaluator requires clarification or further information.

Phase 6. Suggest the term FINALISATION – a term the OTC Section have used to mean the administrative finalisation of the ARTG Entry.

Note: The applicant may choose to withdraw their application at any time.

PHASE 1: Pre-submission meeting

Applicants are encouraged to arrange a meeting with the TGA prior to submitting an application for evaluation of a new registered complementary medicine. The intention of the meeting is to assist the applicant in submitting a high quality dossier. Discussion will focus on the structure of their proposed application, the identification of critical issues and the apparent suitability of the approach proposed by the applicant. It should be noted that no assessment or evaluation of data will be undertaken by the TGA as part of a pre-submission meeting.

There is no fee associated with a pre-submission meeting. Applicants should contact the TGA to arrange the meeting. For more information on the conduct of meetings, refer to the Australian Regulatory Guidelines on Prescription Medicines ~~appendix~~ Guidance 5: ~~'Conduct of meetings between TGA and applicants~~Presubmission meetings with TGA'.

[redacted] It is disappointing to find this guidance is to be kept within ARGPM. Industry were advised that it would be a webpage common to all product types.

[redacted] Updated hyperlink provided.

PHASE 2: Submission of application and payment of application fee

An application for a registration of a complementary medicine is submitted electronically via the TGA's eBusiness services (eBS) portal. Access to eBS requires a user name and password, which is obtained by submitting a 'Client Details Form' followed by an 'eBS Access Request Form'.

An application must be accompanied by an 'application fee' (non refundable) and the dossier. Information on current fees can be found on the TGA website.

The TGA will acknowledge receipt of the application.

PHASE 3: Screening of application, determination and receipt of evaluation fee

The screening of the application consists of an administrative and a technical screen. In general, screening aims to identify an application that is unacceptable for evaluation. That is, the application is considered 'not effective' as determined under 23 (2) of the Act:

> 23 (2) An application is not effective unless:
> (a) the prescribed application fee has been paid; and
> (b) the applicant has delivered to the office to which the application was made such information, in a form approved, in writing, by the Secretary, as will allow the determination of the application; and
> (ba) if the application is for the registration of restricted medicine—the application is accompanied by product information, in relation to the medicine, that is in the form approved under section 7D in relation to the medicine; and
> (c) if the Secretary so requires—the applicant has delivered to the office to which the application was made a reasonable number of samples of the goods.

The screening phase determines that:

- all required fields on the application form have been completed
- the 'application fee' has been paid
- the dossier provides sufficient information; and
- the route of evaluation is appropriate.

[redacted] This should be an efficient, structured check of presence of appropriate information and not a mini-evaluation which duplicates effort and increases evaluation time.

Can a check list be provided so that industry can ensure the information expected is present.

If an application is considered 'not effective' (and therefore not suitable for evaluation as a new registered complementary medicine) the applicant will be informed of the reasons for this decision. Where there are minor errors or omissions that can be readily addressed, the sponsor will be given the opportunity to remedy these. However, absence of data or obvious deficiencies is indicative of an incomplete application.

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A decision that an application is 'not effective' is made under section 23(2) of the Act. As this is not a decision of the Secretary it is not an 'initial decision' under subsection 60(1) of the Act. Therefore the applicant does not have a right of review under section 60 of the Act, but does have a right to apply to the Federal Court on questions of law.

[redacted] The comments in the ARGCM Part D are not correct.

Section 60(1)(c) indicates that a decision under Part 3-2 is an "initial decision". Section 23 is in Part 3-2 of the Act. Thus a decision that an application is not effective is certainly an initial decision and certainly reviewable under section 60.

If the application is considered 'effective' (and therefore, acceptable for evaluation) the TGA determines the 'evaluation fee' payable. The 'evaluation fee' is in addition to the 'application fee' and is based on the number of pages of clinical and nonclinical data submitted (administrative and quality data are excluded from the page count). The following types of safety data count towards the calculation of evaluation fees:

- biological activity/pharmacodynamics
- pharmacokinetics
- animal/toxicological studies
- bioavailability/bioequivalence study
- human data
- published papers and reviews
- meta-analysis reports
- literature search strategy and results
- expert overviews/summaries/reports; and
- case reports and adverse reaction reports

All relevant data should be submitted at the time the application is lodged. The omission of such data may jeopardise the application.

The applicant will be notified in writing by the TGA regarding the acceptance of the application for evaluation and the applicable evaluation fee. The evaluation process will not commence unless the evaluation fee has been paid in full. The application will lapse if evaluation fees are not paid within two months of becoming payable. In this case, the applicant will be notified that the application has lapsed and advised that, should they wish to continue, a new application will be required.

PHASE 4: Evaluation

In the evaluation stage, the quality, safety and efficacy of the proposed new registered medicine are critically assessed and an evaluation report is produced.

Quality

The data are evaluated to determine the quality of the medicine, including the identity, impurities and stability of all ingredients. The assessment also takes into account information about the manufacturing processes and the compliance with good manufacturing practice (GMP). Quality-control measures are assessed to determine if the

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medicine will be produced to a consistent quality. Stability data for the medicine are evaluated to confirm that the medicine is of appropriate quality over its proposed shelf–life.

[redacted] Is this necessary? Quality control is already assured by process validation and GMP..

Safety

History of use, biological activity, toxicology, clinical trials and reports of adverse reactions are assessed to determine the safety of the medicine.

Efficacy

The assessment of the efficacy data includes a detailed evaluation of the proposed indication(s) and any claims that the applicant intends to make for the medicine to determine whether the data supplied adequately support the requested indication(s)/claim(s).

Where the evidence is considered not likely to support the proposed indication, the applicant will be advised in writing and asked whether they wish to amend the indications in line with the available evidence.

[redacted] This is an unusual piece of information here. Will TGA insist on their own interpretation at variance with that of the expert report?

Medicine presentation, consumer medicine information and product information

All aspects of the medicine presentation, including proposed labelling, are assessed for compliance with the various legislative requirements (including advertising requirements) and to ensure clarity is provided for consumers in relation to the medicine and its proposed use.

When ~~provided~~required, Product Information and Consumer Medicine Information are also assessed.

[redacted] Suggest a link to Section 7D of the Act.

During evaluation, the evaluator will identify any matters that require clarification or information, and where necessary a consolidated set of questions will be prepared by the TGA delegate and sent to the sponsor (Section 31 of the *Therapeutic Goods Act 1989*).

The sponsor should respond addressing all issues and questions raised by the delegate. If possible where response relates directly to the content of a module of the submission dossier, the response should be provided in CTD format.

Further clarification may need to be sought to satisfy the Delegate.

Possible consideration by a TGA advisory committee

In some circumstances the Delegate for the Secretary of the Department of Health and Ageing (the Delegate) may seek advice from a TGA advisory committee in relation to the application. In this situation, the applicant is informed that the committee's advice is being sought and they may choose to provide comment for the committee's consideration. Subsequently the applicant will be informed of any relevant advice given by the committee.

PHASE 5: Decision

In making a decision on the application, the Delegate will take into consideration the TGA evaluation report, any advice given by the advisory committee and any subsequent comment provided by the applicant. The decision to register the medicine may be a complex one and is based on the need for the medicine and its benefit-to-risk ratio.

[redacted] This suggests Rx application. Otherwise it insinuates the medicine will not be approved if there is not a need for the medicine. What does this mean? Does it mean that if there are other medicines on the market for the indication it will not be approved?

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The applicant will be advised in writing of the Delegate's decision. If the decision is to reject the application, the letter will provide the reasons for the decision. If the decision is to approve the application, the conditions of registration will be provided.

If the applicant does not agree with the decision of the Delegate, the applicant has the right to appeal under Section 60 of the Act.

PHASE 6: Implementation

The decision letter will include a request for the future sponsor of the medicine to provide assurance that all details of the medicine are correct prior to the medicine being entered on the ARTG by the TGA. After being entered, a registration certificate will be available online for printing by the sponsor. The registration of therapeutic goods begins on the day specified in the certificate of registration and remains valid until suspended or cancelled. Annual renewal charges will apply while the medicine remains registered on the ARTG.

[redacted] Suggest including a statement about the standard and specific conditions of registration and the sponsor's responsibility to maintain the medicine within the conditions during the life of the product.

Information required in an application for evaluation of a new registered medicine

General application format

An application for evaluation of a new registered complementary medicine must include a comprehensive dossier of relevant safety, quality and efficacy data. If provided in hard copy, two copies of the data supporting the application must be provided. Alternatively, if the data is presented in an electronic PDF document (that is searchable and 'copy-enabled'), one copy is sufficient (note that presentation of the data in an electronic format is preferred by the TGA).

[redacted] Were the TGA not aiming for paperless submissions by 2015?

It is recommended that the data in the application be presented in a manner consistent with the European Medicines Agency (EMA) - Common technical document (CTD). The CTD is divided into five modules and is an internationally agreed set of specifications for a submission dossier format:

Module 1:	Administrative information and prescribing information for Australia
Module 2:	Summaries of quality, safety and clinical data
Module 3:	Quality
Module 4:	Nonclinical data
Module 5:	Clinical data

[redacted] Are there any unique requirements for Registered CM products which are not covered?

Although the CTD format is not a mandatory requirement for a new registered complementary medicine application, presentation in this manner will expedite evaluation. However, for some complementary medicine registration applications, not all parts of the CTD modules will be relevant. Where data are not available for a particular CTD heading, a justification must be provided. This may be brief and may be as simple as identifying Not Applicable (N/A) in the Table of Contents.

[redacted] Do you mean not included in the application?

Briefly, the dossier should be presented with:

- a cover ~~page~~ letter outlining the purpose of the application and the full dossier content
- all pages sequentially numbered

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- a table of contents
- the literature search strategy
- all documents, including references, in English and legible. If original documentation is in another language, it should be translated to English by a certified translator and both the English version and the original document should be provided. Non-English documents without certified translations and non-certified translations will not be considered as valid data; and
- an overview (CTD module 2) of presented data for each section of the ~~application~~ application as necessary (CTD modules 3-5 or their equivalents; see below) which provides a critical scientific summary (an Expert Report) explaining how the safety, quality and efficacy of the medicine have been established.

The type of information required in an application for evaluation of a new registered complementary medicine is provided in Tables 1 to 5. For items marked with an asterisk, further details are provided in text below the tables. In addition, comprehensive guidance on data required for quality (Table 3) is provided in Attachment 17.

[redacted] The table below should contain the relevant information briefly provided at the appropriate point within the table, and with links to where more detail can be found. E.g. Literature searches.

Table 1: Administrative information for a new registered complementary medicine application

Administrative information (consistent with CTD Module 1)		
1.0	**Cover letter***	Outlining purpose of application and dossier contents
1.2	**Application form**	Form submitted via the TGA's eBusiness services (eBS) portal
1.1	**Table of contents**	For electronic dossiers, provide hyperlinks to each section of data
1.0	**Request for confidentiality***	Where required
	Proposal for a new ingredient name*	Where an ingredient does not have an approved Australian name
1.5	**Literature search***	Search strategy, results with justification for inclusion/exclusion of data (where relevant)
1.3	**Labelling and packaging***	Drafts provided of all proposed medicine labels and other packaging
1.3	**Australian Product & Consumer Information***	Required for medicines that contain a substance in Schedule 3, 4 or 8 of the Poisons Standard or restricted medicines
1.4	**Expert information***	A curriculum vitae and declaration of any association with applicant or sponsor

[redacted] s is a new tant to make it more approachable.

[redacted] Where does this sit within the Module 1? 1.2?

[redacted] Closing devices?

[redacted] The name, qualifications and role should be sufficient.

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Administrative information (consistent with CTD Module 1)		
1.7	**Good manufacturing practice**	A list of manufacturers with evidence of acceptable GMP- for manufacturers in Australia, this would be the TGA licence number ARGOM Dossier Matrix states [In Australia evidence of GMP is generally not required in module 1.7 (except for active premixes) as it is provided in electronic application]
1.5.3	**Genetically modified organisms***	Notified to the TGA
1.6?	**Ingredients of human or animal origin**	Evidence as to the transmissible spongiform encephalopathy (TSE) safety of the material used Is there a Form for declaration/assurance?
1.10	**Overseas regulatory status***	Country, regulatory status, length of time and volume of supply (where relevant)
1.2	**Pre-submission meetings**	A summary of any pre-submission meeting with the TGA
1.2.3	Patent certificates~~Other information~~	Where available: ~~Patent certificates and information relating to pharmacovigilance~~
1.11	**Summary of Biopharmaceutic Studies**	http://www.tga.gov.au/pdf/forms/pm-forms-bioavailability.pdf
1.13	~~information relating to pharmacovigilance~~	information relating to pharmacovigilance (where relevant). Declaration form in Module 2?

[redacted] As this is a new preferred format, it is important to provide more guidance, to make it more approachable.

[redacted] Both Rx and OTC A request this form be completed to assist finding key data quickly and easily.

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Table 2: Overview and summaries of quality, safety and efficacy data for a new registered complementary medicine application

Overview and summaries of quality, safety and efficacy data (consistent with CTD module 2)		
CTD Module No.	**Medicine details**	
2.1	Table of Contents	
2.2	Introduction	
	Name	Proposed name of medicine

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	Overview and summaries of quality, safety and efficacy data (consistent with CTD module 2)	
	Dosage	Dosage form, range, frequency and duration of use and pack sizes
	Composition	Medicine formulation
	Route of administration	For example: oral, topical
	Container type	For example: ~~plastic~~ PET bottle with child-resistant closure or blister pack in carton
	Proposed therapeutic use	Proposed indications and target population
	History of use	Human exposure data, dietary, traditional and commercial use in Australia and overseas
2.3	**Summary of quality information***	
	A critical scientific summary explaining how the quality of the medicine has been established.	
2.4	**Summary of safety information***	
	A critical scientific summary explaining how the safety of the medicine has been established.	

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Overview and summaries of quality, safety and efficacy data (consistent with CTD module 2)
2.5 Summary of efficacy information*
A critical scientific summary explaining how the efficacy of the medicine has been established.

Table 3: Quality information for a new registered complementary medicine application

Quality information (consistent with CTD Module 3)	
Information on quality for each active ingredient of the medicine	
Nomenclature	Using Australian approved name format
Structural formula	Structural formula of the ingredient and /or components
General properties	Physiochemical and other relevant properties
Manufacturing details	List of manufacturers
	Description of manufacturing process and process controls
	Control of materials
	Control of critical steps and intermediates
	Process validation and/or evaluation
	Manufacturing process development
Characterisation	Elucidation of structure and other characteristics
	Impurities
Control of substances - specifications of raw materials	Specifications providing set of tests and limits
	Analytical procedures and validation
	Batch certificate of analysis
	Justification of specifications

[redacted] Also provide CTD Module numbers for all sections.

[redacted] How will this relate to herbal ingredients?

[redacted] Again, how will herbal ingredients be treated?

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Quality information (consistent with CTD Module 3)	
Reference standard	Reference standards or materials
Container closure system	Details provided on container closure system where this might influence the stability of the active ingredient/s.
Stability of active ingredients	Stability summary and conclusions
	Stability data
Information on quality for the medicine (finished product)	
Description and composition	Name, Dosage form, including any special characteristics, for example: modified release
Medicine development	Formulation of the medicine - table of the active and excipient ingredients and their purpose in the formulation
	Formulation development including a discussion of the studies that led to the proposed dosage form, formulation, method of manufacture and container
	Overages
	Physiochemical and biological properties
	Manufacturing process development
	Container closure system
	Microbiological attributes
	Compatibility
Manufacture of the medicine	Manufacturer name/s
	Batch formula
	Description of manufacturing process and process controls
	Control of critical steps and intermediates
	Process validation and/or evaluation

[redacted] Also provide CTD Module numbers for all sections.

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Quality information (consistent with CTD Module 3)	
Control of excipient/s	Specifications
	Analytical procedures
	Validation of analytical procedures
	Justification of specifications
	Excipients of human or animal origin
	Novel excipients
Control of finished product	Specifications
	Analytical procedures
	Validation of analytical procedures
	Batch analysis
	Characterisation of impurities and impurity requirements for non-pharmacopoeial products
	Justification of specifications
Reference standards or materials	
Container closure system	
Finished product stability	Stability summary and conclusion
	Stability data

[redacted] Also provide CTD Module numbers for all sections.

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Table 4: Nonclinical data for a new registered complementary medicine application

Nonclinical data (addressing safety* and efficacy*)(consistent with CTD Module 4)	
Pharmacology	Primary pharmacodynamics : in vitro and in vivo
	Secondary pharmacodynamics: in vitro and in vivo
	Safety pharmacology
	Pharmacodynamic drug interactions
Pharmacokinetics	Analytical methods and validation reports
	Absorption
	Distribution
	Metabolism
	Excretion
	Pharmacokinetic drug interactions (nonclinical)
	Other pharmacokinetic studies
	Local tolerance studies
	Other toxicity studies: antigenicity, immunotoxicity, mechanistic studies, dependence, metabolite studies, impurities, phototoxicity studies
Toxicology	Single dose toxicity
	Repeat dose toxicity
	Genotoxicity: in vitro and in vivo
	Carcinogenicity: long term studies and short or medium term studies
	Reproductive and developmental toxicity: fertility and early embryonic development, prenatal and postnatal development, studies in offspring
	Local tolerance

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Nonclinical data (addressing safety* and efficacy*)(consistent with CTD Module 4)	
	Other toxicity studies: Antigenicity, immunotoxicity, mechanistic studies, dependence, metabolites, impurities

Table 5: Clinical data for a new registered complementary medicine application

Clinical data (addressing safety and efficacy) (consistent with CTD Module 5)	
Pharmacology studies	Pharmacokinetics Pharmacodynamics
Efficacy studies	Controlled and uncontrolled efficacy clinical trials
	Efficacy-related PI/CMI comments (where applicable)
Safety studies	Controlled and uncontrolled safety clinical trials
	Safety-related PI/CMI comments (where applicable)
	Post-marketing data
Risk-benefit assessment	Included in expert report

[redacted] Why is this here? It should be included in the requirements for the expert reports in Module 2.

Administrative information

Application covering letter

A covering letter should accompany the application providing:

- the purpose of the submission
- the medicine name, active ingredient name(s), dosage forms, strength
- scheduling details from the Poisons Standard, where relevant
- the proposed therapeutic indications
- the number of volumes and a total page count for each module/section of the dossier; and
- the proposed sponsor.

Request for confidentiality for information provided as commercial in confidence (optional)

The *Freedom of Information Act 1982* (the FOI Act) aims to promote public access to information held by Commonwealth authorities and to consider such information as a

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national resource. Under the FOI Act, persons may request access to documents held by the TGA.

Applicants (for the evaluation of a new registered complementary medicine) may request that data contained in their application remain confidential in the event that a request is made under the provisions of the FOI Act. Section 45 (1) of the FOI Act enables 'documents containing material obtained in confidence' to be exempt from release under the FOI Act if disclosure under the FOI Act would found an action by a person for breach of confidence.

When information that is already public knowledge, for example: information contained in a patent application or appearing in a published article, the information cannot be claimed to be confidential.

Confidentiality statements accompanying applications must be consistent with the powers and duties of the Secretary under the Act. Examples of acceptable confidentiality statements are:

> 'All and any information contained in this document is to be regarded as a trade secret because the document contains unpublished details and results of private research proprietary to [name of company or applicant], the disclosure of which to its competitors could be disadvantageous'.
>
> 'All and any information contained in this document is to be regarded as commercial or financial information that is privileged or confidential in that it contains valuable data or information which is used in the business of [name of company or applicant] and is of a type customarily used in confidence, or regarded as privileged, and has not been disclosed to any member of the public by [name of company or applicant]'.

A confidentiality statement will only be accepted as an assertion by a company (commercial-in-confidence) and requests received under the FOI Act may need further evidence of confidentiality from the company to assist with the decisions on whether to release specific documents and information. The TGA is not the final arbiter of whether a document is exempt from disclosure under the FOI Act. When an FOI request is received, the TGA will consult the applicant who submitted the information in order to:

- seek the applicant's views on the release of the document containing the information, and if the applicant believes it should be exempt, the reasons for claiming exemption; and
- give the applicant the opportunity to request an internal review or a review by the Australian Information Commissioner of any TGA decision to release the information related to the applicant under the terms of the FOI Act.

Proposal for new ingredient name/s

All the components of the proposed medicine should be identified using Australian approved terminology. The TGA approved terminology for medicines publication provides approved terminology for substances, containers, dosage forms, routes of administration and units of measurement.

Where the proposed new registered complementary medicine includes an ingredient that does not have an approved name, a proposal for a new name is required to be submitted with the application. The various forms for this purpose are available on the TGA's website.

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Australian labelling and packaging

Applicants should include drafts of all medicine labelling in the application. Artwork ready for printing or examples of the printed labels are preferred. If only the draft label text is submitted, the size, colour and positioning of the text on the label should be made clear. This information is necessary to assess compliance with the various legislative requirements. Where draft labelling is submitted, it is usually a condition of registration that final printed labels be provided to, and approved by, the TGA prior to supply of the medicine.

[redacted]

The cost of plates which will then have to be changed to add the AUST R plus the cost of a small label run would be prohibitive.

Where the pack sizes differ but the label is to remain the same (and the applicant gives an assurance to that effect) only one set of labels is required in the application. An assurance that the text size is also identical must also be included. If the text size is different for pack sizes, or if the presentation of the information is different, the label for the additional pack size must be submitted.

Labelling must comply with the legislation and with the current version of Therapeutic Goods Order No 69 – General requirements for labelling of medicines (TGO 69). Attachment 10 provides a guide to assist with compliance with various legislative requirements.

[redacted] To be updated we assume.

Proposed Australian Product Information and Consumer Medicine Information

A Product information (PI) document is required for restricted medicines (refer to section 25AA of the Act). The Restricted Medicine Specification 2011 [an instrument made under section 3 (2A) or 3(2B) of the Act] lists the medicines or classes of medicine that are to be 'restricted medicines' for which a draft PI document is required as part of the submission dossier:

- medicines subject to Schedule 3 of the Poisons Standard; and
- Part 1 of Schedule 10 to the Regulations other than in items 1(b) and 14.

The PI contains technical information intended for healthcare practitioners and must not include promotional material. Refer to Product information on the TGA website for more information on providing product information.

Regulation 9A of the Regulations states that a Consumer Medicine Information (CMI) document is required for therapeutic goods included in Part 1 of Schedule 10 to the Regulations and medicines subject to Schedule 3 of the Poisons Standard. The CMI must comply with the requirements specified in Schedule 13 of the Regulations, although the information does not have to be set out as listed there. The CMI contains general information about the medicine, written in plain English, intended for the consumer and cannot include promotional material.

An applicant may choose to include a PI or CMI document for their new registered complementary medicine where there is no legal requirement for these. In these instances, the requirements for the documents are the same as outlined above.

Information about the expert/s

[redacted] It would be useful if OCM could provide advice of when this is really necessary. E.g. NCE/new route of administration/modified release/New combination/New indication.

But is this really necessary for a Multivitamin/multimineral supplement making no new indications, but registrable solely on the basis of schedule of an ingredient?

The author of an Expert Report (see below: 'Summaries of quality, safety and efficacy data'), who may be employed by the sponsor, should be a person with appropriate qualifications and experience. The expert's curriculum vitae should be included in the 'Administrative' part of the application. The expert should also provide a statement declaring the extent, if any, of their professional or other involvement with the dossier owner and confirm that the report has been prepared by them or if not, any assistance provided and by whom. Module 1.4 of the CTD document modified for Australia 'Module 1

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– Administrative information and prescribing information for Australia' contains a pro-forma for supplying information about the expert.

Literature search strategy

In addition to providing the literature search strategy (refer to Attachment 16: 'Choosing literature for evaluation and evaluating search strategies'), the reasons for the inclusion or non-inclusion of any material should be provided. Applicants should also be aware of the TGA guideline: Literature based submissions - points to consider.

Information on genetically modified organisms

The applicant should advise the TGA if the proposed new registered complementary medicine includes a substance that is, or is obtained from, a genetically modified organism. The nationally consistent legislative scheme for regulating gene technology comprises the Commonwealth *Gene Technology Act 2000*, the Gene Technology Regulations 2001 and corresponding State and Territory legislation (refer to the Office of the Gene Technology Regulator website).

The TGA will assess the safety, quality and efficacy of a genetically modified organism or material by the same means as for any other substance included in the proposed registered complementary medicine.

If the medicine is approved, the TGA is obliged to notify the OGTR.

Information on overseas regulatory status

If the product is supplied in other countries, the country, approval date (or date and length of time of supply) and the regulatory status (for example: dietary supplement) should be stated. Provision of documentation detailing the annual sales volume and estimates of the size of the exposure population is not mandatory, but this is considered to be supporting data and will assist the assessment of the application. If an application for the product has been made to a regulatory authority in any other country, this should be stated, as well as the outcome of that application, that is: approval or rejection.

[redacted] Do you need to clarify that this applies to the SAME product as opposed to a similar ? E.g. for a multivitamin will the sponsor be able to provide data on competitors' similar products?

[redacted] Duplication

Summaries of quality, safety and efficacy data

The application should include Expert Reports, cross-referenced by page number to the submission, providing separate critical appraisals of the quality and manufacturing, nonclinical and clinical efficacy and safety of the medicine.

[redacted] Or hyperlinked

Guidance on the content and format of Expert Reports may be found in Module 2 of the Common Technical Document (CTD).

The overview of the clinical data should discuss both positive and negative outcomes and should explain how the data support the proposed indications and claims. Where more than one indication is proposed, each indication should be separately justified. In establishing the safety profile of the medicine, the nonclinical and clinical data should be summarised and discussed. Adverse events (both serious and non-serious) should be discussed noting any causal relationships.

Data provided on quality

Quality data should be presented consistent with the CTD Module 3 (Table 3 above). Attachment 17 provides additional guidance on the quality issues for ingredients and the medicine that should be addressed in an application for a new registered complementary medicine.

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Data provided on safety and efficacy (nonclinical and clinical data)

Safety and efficacy data should be presented as 'nonclinical' and 'clinical' data modules (consistent with the CTD Modules 4 & 5) (Tables 4 and 5 above).

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 medication/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.

Traditional use

Traditional use cannot fully establish the safety and efficacy of a proposed new registered complementary medicine. However, traditional, long-term and safe therapeutic use may be taken into account in evaluating the safety of a medicine.

Where evidence of traditional use is provided in the dossier, it must be demonstrated that the proposed medicine is consistent with the traditional preparation and the traditional use (including dose, route of administration and duration of use).

Well documented ingredients/medicines

[redacted] We have inserted some examples of generally accepted reference texts.

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 some OTC medicine applications, evidence to support safety and efficacy may be found in standard reference texts. Where this is the case, further information on the safety and efficacy of the product may not be required.

Applications based on standard reference texts should include an overview or covering letter referring to the texts and detailing their relevance (copies of the relevant pages should be provided).

The following are examples of reference texts which are usually acceptable as sources of information on the safety, efficacy and dosage regimen of ingredients in ~~an OTC~~non-prescription medicines:

- Handbook of Non-prescription Drugs, American Pharmacists Association, USA
- Martindale: The Complete Drug Reference, Sweetman SC (Ed.), Pharmaceutical Press, UK

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- Remington: The Science and Practice of Pharmacy, Gennaro AR (Ed.), Lippincott Williams & Wilkins, USA
- Handbook of Pharmaceutical Excipients, Kibbe AH (Ed.), American Pharmacists Association, USA and Pharmaceutical Press, UK
- AHFS Drug Information, McEvoy GK (Ed.), American Society of Health System Pharmacists, USA
- Meyler's side effects of drugs; Dukes MNG et al. (Eds), Elsevier

It would be helpful to provide clear guidance on acceptable versus non-acceptable reference texts, and at least a preliminary list of acceptable references. We have included a selection here as a suggested starting point.

- Allen. HC (1936) Keynotes And Characteristics With Comparisons of Some of the Leading Remedies of the Materia Medica. 8th ed. Boericke & Tafel.
- Australian Government Dept. of Health and Aging. 2006. Nutrient Reference Values for Australia and New Zealand including Recommended Dietary Intakes.
- Battaglia S. 1995. The Complete Guide to Aromatherapy. The Perfect Potion Press.
- Bensky D and Gamble A. 1986. Chinese Herbal Medicine Materia Medica. Eastland Press.
- Blumenthal M. 2003. The ABC Clinical Guide to Herbs. American Botanical Council/ Thieme.
- Blumenthal M. Goldberg A. Brinckmann J et al. 2000. Herbal Medicine. Expanded Commission E Monographs. Integrative Medicine Communications.
- Boericke W (1927) Pocket Manual of Homoeopathic Materia Medica. Comprising The Characteristic And Guiding Symptoms Of All Remedies (Clinical And Pathogenetic). Boericke and Runyon Inc. New York. USA.
- Boger CM (1992) Boenninghausen's Characteristics Materia Medica and Repertory with Word Index. Jain Publishing. New Delhi.
- Braun L and Cohen M. 2010. Herbs & Natural Supplements. An Evidence-Based Guide. 3rd Ed. Churchill Livingstone / Elsevier.
- Buckle J. 2003. Clinical Aromatherapy. Essential Oils in Practice. 2nd Edition. Churchill Livingstone.
- Grieve M. 1971. A Modern Herbal. Dover.
- Gruenwald J. Brendler T. Jaenicke C. 2000. Physicians' Desk Reference for Herbal Medicines. 2nd ed. Medical Economics Company.
- Hempen, C-H and Fischer T. 2007. A Materia Medica for Chinese Medicine, 2nd Edition. Churchill Livingstone/Elsevier.
- Hendler S. Rorvik D. Fleming T et al. 2001. PDR for Nutritional Supplements. 1st ed. Medical Economics / Thomson Healthcare.
- Julian OA (1979) Materia Medica of New Homoeopathic Remedies. Beaconsfield. Bucks. UK.
- Kent JT (1935) Repertory of the Homoeopathic Materia Medica. Enrart & Karl. Chicago.
- Kent JT (1978) Repertory of the Homoeopathic Materia Medica. 6th American edition. Jain Publishing. New Delhi.
- Mahan LK and Escott-Stump S. 2008. Krause's Food and Nutrition Therapy. 12th ed. Saunders.
- Mills S and Bone K. 2000. Principles and Practice of Phytotherapy. Churchill Livingstone.
- Monographs on Selected Medicinal Plants. WHO.

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- Nadkarni A. 1999. Indian Materia Medica. Popular Prakashan.
- Price S and Price P. 1999. Aromatherapy for Health Professionals. 2nd. Ed. Churchill Livingstone.
- Schilcher S. 1997. Phytotherapy in Paediatrics. Medpharm.
- Shils M. Shike M. Ross A et al. 2006. Modern Nutrition in Health and disease. 10th Ed. Lippincott Williams & Wilkins.
- The Scientific Committee. 1983. British Herbal Pharmacopoeia. The British Herbal Medicine Association.
- Tierra M and Tierra L. 1998. Chinese Traditional Herbal Medicine. vol. 2. Lotus Press.
- Wahlqvist. M 2002. Food and Nutrition. Australasia. Asia and the Pacific. 2nd Ed. Allen and Unwin.
- Weiss R. 1988. Herbal Medicine. Beaconsfield Arcanum.
- WHO and FAO. 2004. Vitamin and Mineral Requirements in Human Nutrition. Second Edition.
- Williamson E. 2002. Major Herbs of Ayurveda. Churchill Livingstone.

Current editions should be referenced unless otherwise justified. Note that limited clinical reports of efficacy alone or anecdotal reports (e.g. in Martindale "*xxxx has also been used in* ...") are not regarded as adequate evidence of safety and efficacy.

Literature based submissions

In circumstances where the sponsor lacks supportive data of their own but considers available published scientific literature to be supportive, it may be appropriate to submit a 'literature-based submission'. This option may be appropriate for applications such as changes to indications or directions for use or less commonly for new product applications. The supporting literature must be appropriately relevant to the application – for example the information should generally relate closely to the formulation, dosage regimen and indications of the proposed product.

A literature-based submission should represent a comprehensive and unbiased review of the available literature in relation to the application using a medical/scientific database such as Medline. For older medicines or where relevant reports are few, the search may need to include all records in Medline and/or other databases such as Embase. To enable critical analysis or duplication of the search by the TGA, details of the search strategy and search output should be included (electronically on CD/DVD, as well as hard copy) in the application. The search output should be annotated to include those papers selected for inclusion in the submission and cross-referenced to the overview. A list or table of reports which have been excluded from consideration should be presented together with reasons for exclusion. All submitted data/papers etc. should be page numbered.

Published reports of clinical trials should only be included in the submission where:

- the trials are conducted using the same active ingredient(s) with the same dosage concentration, a similar dosage regimen, dosage form, route of administration and indications to the product proposed for registration;

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- the trials are reported in sufficient detail to allow an independent assessment of the results (including methods and a statistical analysis of the results) in relation to the safety and efficacy of the product proposed for registration.

Trials should be excluded if they are not consistent with the above, or if they are poorly conducted or reported, or not of sufficient power to produce statistically significant results. All relevant, well-conducted and reported trials should be included regardless of whether the findings are adverse to the product proposed for registration. For relevant trials which are reported in a language other than English, a certified translation should be provided.

Well conducted, published reviews may be of assistance as supporting material and should be included where relevant.

A literature-based submission must include an overview, which includes a **critical appraisal of *all* the papers submitted**.

The overview should include the reasons for selecting and excluding retrieved published papers and refer to the selection criteria used. Issues such as publication bias and potential duplication of data from the same subjects in different papers should be discussed where relevant.

The overview should also include a comprehensive appraisal of the quality of all the papers submitted, the quality of the clinical trials reported in those papers, and the quality of the data generated. Studies considered to be pivotal should be identified and a rationale provided. Data from randomised, double blind, controlled studies would be expected to be given greater weight than data from non-randomised, uncontrolled or open studies. The papers need to be discussed individually and collectively in terms of the weight of evidence they provide. Implications of any differences in formulation used in the literature reports should be discussed.

A table should also be included giving summary details of all reports which are present in the submission including:

- abbreviated publication details (author(s) and journal reference) where relevant;
- the type of study or report (e.g. double blind, randomised, multi-centre, cross-over trial);
- the number of subjects included in the trial;
- treatment details, including details of the dosage form, formulation, dosage schedule and treatment duration;
- parameters studied; and
- summary of results in relation to efficacy and safety.

With regard to safety data, there should be tabulation and analysis of all adverse events (including abnormal laboratory values, medicine interactions etc.) for all documented clinical studies and any adverse events which have been reported to the sponsor. Further guidance on literature-based submissions may be found on the TGA website.

Clinical Trials

In circumstances where safety and efficacy data are required but neither standard references nor a literature-based submission are appropriate, it will be necessary to

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provide reports of clinical trials that the sponsor has conducted to establish the safety and efficacy of the product proposed for registration.

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 is intended to provide a critical analysis of the clinical data in the dossier while the clinical summary is intended to provide a detailed, factual summarisation of all of the clinical information provided.

Postmarketing data

The application should include all relevant postmarket data, including published and unpublished data.

If marketed overseas, details of the number of people estimated to have been exposed to the medicine since the start of supply should be provided and categorised, as appropriate, by indication, dosage, route of administration, treatment duration and geographical location. Any safety issues identified following marketing should be highlighted and any regulatory action relating to safety taken by an overseas regulatory agency should be detailed.

[redacted] Duplication?

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.

Postmarket vigilance of registered complementary medicines

The TGA adopts a risk management approach to regulating therapeutic goods. Once a therapeutic product is approved, the TGA continues to monitor the product in the market through therapeutic product vigilance activities. TGA postmarket monitoring activities for registered complementary medicines include those listed below.

Monitoring and assessment of adverse events

Section 29A of the Act requires sponsors of medicines registered or listed in ARTG to report adverse reactions about which they become aware. The Australian guideline for pharmacovigilance responsibilities of sponsors of medicines sets out requirements and guidance for the reporting of adverse reactions and significant safety issues for both registered and listed medicines regulated by the TGA. In addition, adverse events are reported to the TGA by a variety of other sources including: consumers, health professionals, hospitals and pharmacies.

Inspection of manufacturers

Manufacturers of therapeutic goods supplied in Australia are subject to regular inspections by the TGA's Office of Manufacturing Quality. Details of the requirements for the manufacture of medicines are specified in the PIC/S Guide for Good Manufacturing Practice for Medicinal Products. For more information regarding the GMP inspection of medicine manufacturers please refer to 'audit of medicine manufacturers'.

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Sampling of medicines in the marketplace

The TGA undertakes a laboratory testing program which prioritises therapeutic goods considered to carry a higher risk, while still allowing for responsive testing for issues arising in the marketplace, for example: adverse events and complaints about specific medicines. The testing program involves the selection of both random and targeted samples for analysis. Samples for the testing program are obtained from manufacturers, wholesalers, pharmacies, hospitals, retail outlets or consumers. For more information on the laboratory testing program, refer to the Office of Laboratories and Scientific Services (OLSS) activities.

Investigations of potential non compliance with the legislation

Investigations of potential non compliance with legislation for registered complementary medicines may be initiated on the basis of:

- a complaint from the public, healthcare practitioners, industry
- issues identified within the TGA
- referral from another Australian agency, for example: the Australian Quarantine and Inspection Service or Australian Customs; and/or
- referral from a related international agency.

Recalls of therapeutic goods

[redacted] Responsibilities of sponsor?

A product recall is the removal of therapeutic goods from supply on the Australian market for reasons relating to their quality, efficacy or safety. Recall of any distributed goods is required whenever public safety is at risk as a result of product noncompliance. A recall can occur because of problems such as: labelling or packaging errors; contamination issues; or an increase in unexpected side effects. Further information on recalls of therapeutic goods is provided on the TGA website: About recalls.

Changes to registered complementary medicines

Following the inclusion of a registered medicine on the ARTG, sponsors may wish to change certain details held by the TGA for that medicine. Factors such as product stability, manufacturer changes and developing marketing strategies may dictate changes to the product details approved at the time of the product's registration on the ARTG.

Section 29A of the Act requires sponsors to notify the TGA of any changes in the information previously provided to the TGA in relation to their therapeutic good. However, in recognition that some changes are minor in nature and actually improve the quality and safety of a medicine, specific changes (refer to Attachments 18A and 18B) are not required to be notified to the TGA, for example: additional analytical tests or tightening of product specifications.

For other changes, there are provisions in the legislation for certain details [that will not make the medicine 'separate or distinct' (refer to Section 16 (1) of the Act)] to be amended in a medicines' ARTG entry, upon request by the sponsor, and maintain the same AUST R number. Section 9D (1), (2) and (3) of the Act provides the circumstances under which a sponsor may request an amendment to the ARTG entry of their medicine.

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Where the proposed change to the medicine will result in a goods that are considered 'separate and distinct' from the existing goods, applicants are required to submit a new application for registration of the medicine, which will result in a new AUST R number. However, in certain circumstances, the new medicine will be 'grouped' under the ARTG entry of the existing medicine and assigned the same AUST R number. The Therapeutic Goods (Groups) Order No. 1 of 2001 (Groups Order) provides the criteria whereby a 'new' medicine will be 'grouped' under the existing medicine's ARTG entry (pursuant to section 27 of the Act).

All applications for changes to registered complementary medicines attract a fee. Information on current fees is available on the TGA website. Regulation 45 of the Regulations provides for the waiver or reduction of evaluation fees under certain circumstances.

Attachments 18A and 18B provide~~s~~ further information on changes to registered complementary medicines.

General comments on changes:

We are disappointed to find that timelines for changes are not mentioned in this draft Guideline.

There needs to be clear guidance on the different types of changes, ie self-assessable and notifiable, vs those requiring assessment, in order to minimise the need for sponsors to seek advice from the TGA.

Firm timelines are needed especially for notifiable changes, which are by definition minor and have no effect on safety. There is no need for evaluation and therefore no justification for delay in finalising the administrative changes to the ARTG.

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Attachments 1 to 7: Under TGA review

Attachments 1 to 7 have previously been released for consultation and are currently under review by the TGA.

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Attachment 8: Finished product specifications, certificate of analysis

Finished product specifications

Note: This attachment was previously released with ARGCM Part B as Attachment 7D. It has been revised to only include information relevant to product specifications. Information on quality data requirements has been incorporated into Attachment 17 'Information on QUALITY required for an application for a new REGISTERED complementary medicine'.

The finished product specification is the set of tests and limits applicable to the finished medicinal product in order to ensure that every batch is of satisfactory and consistent quality at release and throughout its shelf life. The specifications should include all critical parameters in which variations would be likely to affect the safety or efficacy of the product, for example: assay.

The specifications against which a finished product is tested before release for sale are referred to as the 'batch release specifications'. The specifications against which a finished product is tested to ensure satisfactory quality throughout its shelf life are referred to as the 'expiry specifications'. The product, if tested at any time within its shelf life, must comply with the requirements in the expiry specifications.

'Note for guidance on specifications: test procedures and acceptance criteria for herbal drugs, herbal drug preparations and herbal medicinal products' has been adopted by the TGA and provides general principles for setting and justification of a uniform set of specifications for finished products containing ingredient/s of herbal origin.

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

The standards recognised under the *Therapeutic Goods Act 1989* (the Act) are those made by the Minister under Section 10 of the Act (Therapeutic Goods Orders) and the default standards, which currently are relevant statements in monographs in any of the following: British Pharmacopoeia (BP), European Pharmacopoeia (Ph. Eur.) or the United States Pharmacopeia – National Formulary(USP). It should be noted that any matter specified in an order under section 10 of the Act has precedence over requirements of the default standards.

The general monographs of the BP, Ph. Eur. and USP are also relevant, for example: the BP monographs 'Herbal Drugs', 'Herbal Drug Preparations' and 'Extracts'.

The most recent edition of the cited pharmacopoeia should be used.

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), a consent to supply the product is required (refer to ARGCM Part B 'Consent to supply goods that are not compliant with certain legislative requirements').

Information required for a finished product specification

Product details

- name of product
- product code
- date of specification
- revision or version number
- a table listing the tests performed, the expiry requirements or acceptance criteria for the tests (and where different, the release requirements) and reference to the test method (for example: BP HPLC method, 'in-house' TLC method).The tests performed should include the following:
  - appearance of the product [note that the requirements should include: a description of the type of dosage form and any special characteristics (for example: modified release)]
  - physical tests including: average weight, uniformity of weight/ content, disintegration/dissolution (where relevant)
  - chemical tests, including: identification, assay, related substances (where relevant)
  - the microbiological tests
  - any other tests
- a statement of whether all the tests are performed on each batch of finished product; and if not, what tests are performed on rotation and the frequency.
- For listed medicines only, 'Quantified by input' may be applicable, refer to ARGCM Attachments relating to QBI (under review).

Certificate of analysis for finished products

Previously published with Part B: Listed medicines as Attachment 7f.

A certificate of analysis (used for 'release for supply' purposes) is a document certified as a truthful statement of the tests and test results for an individual, manufactured batch of a particular finished product.

Information required for a certificate of analysis

- the manufacturer
- the product name
- the batch number of the product
- the date of manufacture of the batch, the date of the testing and the date of the certificate
- the tests, the tests results, acceptance criteria and a reference to each test method

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- the signature of the appropriate company official.

Attachment 10: Complementary medicine labels

Attachment previously released with the ARGCM Part B consultation as Attachment 8. Information has been revised to be applicable for registered and listed complementary medicines, repetitive information has been removed and a table of required information on a medicine label provided as a guidance tool.

Medicine labels for listed medicines are not submitted to the TGA at the time of listing *via* ELF and are therefore not approved by the TGA. However, listed medicine labels may be reviewed as part of the TGA's random and targeted compliance reviews (see ARGCM Part B: 'Listing compliance reviews').

Medicine labels for registered complementary medicines are evaluated by the TGA. In evaluating a new registered complementary medicine (and in a listing compliance review for listed complementary medicines) all aspects of the medicine presentation, including proposed labelling, are assessed for compliance with the various legislative requirements (including advertising requirements) and to ensure clarity is provided for consumers in relation to the medicine and its proposed use. Copies of all draft product labels (including package insert) should be provided with applications to register new products or vary the labelling of current products. Where the only difference in labelling between pack sizes is the quantity, only one set of labels need to be submitted, provided that an assurance to that effect is supplied with the application.

If possible, full scale, full colour draft labels or mock-ups of the proposed pack should be provided with the registration application to allow a thorough assessment of the product's presentation. If colour labels cannot be provided at the time of submission of the application, text or black and white label mock-ups should be provided. However, colour draft labels will be required for evaluation prior to approval of the product.

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Requirements for medicine labels

The Therapeutic Goods Order No 69- General requirements for labels of medicines (TGO 69 (TGO 69) provides the following definition:

> 'label' means a display of printed information upon, or securely affixed to, the container and any primary pack containing the goods.

A product's 'label' includes the label attached to the container (for example: bottle, tube, sachet or blister pack) and the primary pack (for example: carton). Sponsors must ensure the product label and any printed information supplied with the medicine (for example: a package insert) complies with all relevant legislation, including advertising requirements. Specific documents relating to medicine labelling requirements include:

- The Therapeutic Goods Order No. 69 — General requirements for labels for medicines (TGO 69) (and amendments TGO 69A, TGO 69B and TGO 69C)

- Part 5-1 (Advertising and generic information) of the *Therapeutic Goods Act 1989* (the Act) and the Therapeutic Goods Advertising Code 2007 (TGAC)
- The Therapeutic Goods Regulations 1990 (the Regulations)
- The Required advisory statements for medicine labels (RASML)
- The Standard for the Uniform Scheduling of Medicines and Poisons (the Poisons Standard) (note Australian states and territories vary in the way they adopt the Poisons Standard)
- The TGA approved terminology for medicines
- Listed complementary medicines, must also comply with any conditions of listing (see 'Conditions of listing' ARGCM Part B). Table 1 provides useful guidance for applicants/sponsors on the requirements for medicine labels. Note it is the sponsor's responsibility to ensure their medicine complies with all legislative requirements.

Table 1: Information required on a medicine label

[redacted] Why is this here? Should there not be a link to the current TGO? Please see comments re changes to the requirements made in this document.

[redacted] Number of the requirements of this table are inconsistent with TGO 69. Multiple corrections are required.

Requirements		Relevant legislation
General label requirements		
Text	All mandatory information legible, durable and written in clear and easily understood English. Text in languages other than English may be included on labels, provided they are not misleading or breach the legislation.	Subsection 3(5) of the Act TGO 69 TGAC Regulations 3A, 15(1)(b) and (c) of the Regulations
	Text height of required particulars is ≥ 1.5 mm AUST L or AUST R ≥ 1mm	
	Other text and graphics are acceptable	
Name of the medicine	Included on main label	Subsection 3(5) and 16(1A) of the Act TGO69 TGAC
	Consistent with ARTG entry	
	Appropriate (acceptable presentation)	
	Name clearly distinguishable from other products.	
AUST L or AUST R number	Displayed on main label of primary pack (or immediate container if no primary pack)	Regulation 15(1)(b) and (c) of the Regulations TGO 69

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Requirements		Relevant legislation
Quantity of goods	Displayed on main label	TGO 69
Dosage form	Displayed on main label	TGO 69 TGA approved terminology for medicines
	Provided in correct terminology	
Name and Australian address of sponsor/supplier	Displayed on label	TGO 69
	For blister packs: only name or trademark required	
Batch No.	Displayed on label with correct prefix (Where labels are provided that are not part of a released batch and therefore do not have the batch number, space is provided for Batch No)	TGO 69
Expiry date	Displayed on main label with correct prefix (Where labels are provided that are not part of a released batch and therefore do not have an expiry date, space is provided for expiry date)	TGO 69
Storage conditions	Displayed on main label	TGO 69
Directions for use	Displayed on main label	TGO 69
	Appropriate (method, dose and frequency of administration)	
	Clearly identifies the dose for each target population	
	Where applicable, directions refer to metric measurements (use of culinary measurements, such as '1 tablespoon' is not appropriate)	
Statements of goods purpose/ indications/claims	For an AUST L, present and consistent with ARTG record	Subsection 28(5)(ab) of the Act TGO 69 TGAC
	For an AUST R, as approved by the TGA.	
	Appropriate, not misleading	

[redacted] TGO 69 requires that this appear on the label – it does NOT specify the MAIN label.

Note the definition in TGO 69:
'**label**' means a display of printed information upon, or securely affixed to, the container and any primary pack containing the goods.
That is, the label includes printed information anywhere on the pack.

This is an example of the dangers of re-wording or re-interpreting requirements.

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Requirements		Relevant legislation
Ingredients		
Active ingredients	All included on the main label unless subclause 3(3) or 3(11) of TGO 69 applies.	Schedule 4, part 5, Division 2 to the Regulations Schedule 2 to the Regulations TGO 69 The Poisons Standard TGA approved terminology for medicines
	In correct Australian Approved Names	
	Quantity/ proportion on main label unless subclause 3(3) or 3(11) of TGO 69 applies.	
	Use correct expression and units	
	For an AUST L: compliant with quantity restrictions e.g. organic forms of chromium, vitamin A, KCl and iron	
Herbal ingredients	Complies with specific requirements	Subclause 4(11) of TGO 69
Vitamin ingredients	Complies with specific requirements	Subclause 4(13) of TGO 69
Mineral ingredients	Complies with specific requirements	Subclause 4(12) of TGO 69
Biological ingredients	Complies with specific requirements	TGO 69
Excipient ingredients	TGO 69 First Schedule excipient ingredients declared on label (including those included in proprietary ingredients) for example: lactose	TGO 69
	The selective disclosure of an individual excipient on a medicine label is generally not acceptable. Quantitative or qualitative statements on the medicine label of all excipient ingredients in the product are permitted.	
Preservative/ antimicrobial agents	Name included for any topical preparations	TGO 69
Statements		

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Requirements		Relevant legislation
All statements	Consistent with general principles of the TGAC	Subsections 42DD and 42DL(1)(f of the Act Subsections 4 of the TGAC
	No references to restricted representations (e.g. treatment of IBS) on label (if so, approval /exemption is required by TGA Advertising for the medicine)	
	Comparisons must be factual, balanced and not misleading	
	Must not contain or imply endorsement of the product except as permitted by the TGAC.	
Required representations and required warning statements	Present	The Poisons Standard Schedule 2 and Schedule 4, Part 4, Division 2 and Schedule 4, Part 5, Division 3 of the Regulations TGO 69 RASML Pregnancy warnings? Prescribing medicines in pregnancy database
	Correct statement and presentation	
Negative disclosure statements, eg: 'Free from…'	Accurate and not misleading	Subsection 3(5) of the Act TGAC

ARGOM Provides Guidance beyond the restating of the TGO 69 eg.

Graphics, logos and symbols

Non-corporate graphics, logos or symbols on labels should be consistent with the product's approved details, including being appropriate for the claimed therapeutic use of the product. For example:

- an illustration of a baby would be inappropriate for a product with a dose range starting at 2 years;
- a graphic highlighting joints would be inappropriate for a product that is indicated for use only on soft tissue injuries.

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Reference to other products

Situations where other products may be referred to in labelling include:

- reference to more suitable dosage forms within the same range for different age groups (see ARGOM Appendix 5 Guidelines on OTC applications for specific products: Paediatric products - Solid dose products)
- reference to another product that can be used in conjunction with the product, where appropriate
- reference to a sponsor's other products within the same product range that have the same trade name as the current product, where appropriate.

Note: The products referred to must be approved for supply in Australia.

References to other products which are capable of confusing the consumer (e.g. inclusion on the front panel of a label of the statement '*from the makers of Xxx*' or that it has '*the same active ingredient as Xxx*' may lead some consumers to think the product ***is*** 'Xxx') ~~is~~are unacceptable.

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Comparison

Statements comparing a product with other products or treatments will only be accepted where satisfactory evidence is provided to support the claim. These claims must also comply with Clause 4.5 of the Therapeutic Goods Advertising Code . See also the ASMI Code of Practice, clauses 5.1.3 and 5.2.

Endorsements

Labels must not contain or imply endorsement of the product except as permitted by the Therapeutic Goods Advertising Code (Clause 4.6).

The sponsor should remove an endorsement from the labelling (by way of a notification application to the TGA) once the endorsement is no longer applicable.

Sponsorship

Labels may include reference to sponsorship of the product (e.g. Pink Ribbon Campaign, Cancer Council Australia, Surf Life Saving Australia) when in compliance with clause 4.6 of the Therapeutic Goods Advertising Code. Sponsors should provide evidence that claims relating to any such sponsorship are true, for example, a letter from the relevant organisation showing that claims relating to any such sponsorship are true.

Where the sponsorship includes a potential restricted representation, e.g. Cancer Council Australia, prior approval for the use of the restricted representation must be sought in writing from the TGA.

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Internet addresses

The inclusion of internet addresses on labelling is only acceptable if the sponsor provides an assurance that the information about the product included on the website (including any direct links from that website) is consistent with the information approved by the TGA for that product. If such an assurance cannot be provided, the internet address should be deleted from the labelling.

International labels

Products that are supplied in Australia and also exported to another country may include overseas product registration numbers required by the importing country. Labels intended for export only should be submitted to the Exports Section of the TGA.

Foreign language text on labels

For labels on medicines supplied in Australia a certified English translation of any other language must be provided to verify that the text is consistent with the English language text and that the label, including the product name, does not include or imply any additional indications.

Package inserts

Package inserts are considered part of product labelling (refer to the definition of 'Label' in the Act) and require approval by the TGA. A package insert should be provided if the primary pack label does not contain all the information which the TGA considers to be necessary for the safe and appropriate use of the product by the majority of consumers (including indications, directions for use, and important contraindications and precautions). The TGA may request the provision of a package insert in cases where this applies, if the sponsor has not already submitted a package insert.

A package insert may be in the form of a consumer medicine information (CMI) document if there is an approved product information (PI) document for the product (refer to 'Section 4 Product information' and 'Section 5 Consumer medicine information').

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Attachments 11 to 16: Under TGA review

Previously published for consultation- under TGA review

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Attachment 17: Information on QUALITY required for an application for a new REGISTERED complementary medicine

Presentation of quality data in an application for a new registered complementary medicine

The data on quality in an application for evaluation of a new registered complementary medicine should be presented in a manner consistent with the European Medicines Agency (EMA) Common Technical Document (CTD) module 3: 'ICH M4Q Common Technical Document for the registration of pharmaceuticals for human use - Quality'. While presentation of data in the CTD format is not mandatory, it is encouraged.

Quality aspects to be addressed

For an application for a new registered complementary medicine, quality issues relating to the active ingredient/s and the finished product should be addressed. A list of the European Union guidelines on quality matters that have been adopted in Australia is available on the TGA website.

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

Active ingredient/s

The submitted data required for the active ingredient/s is/are comparable to those required for an application for a new complementary medicine substance. Applicants should refer to 'Attachment 13 Evaluation of complementary medicine substances' for guidance' on the type and detail of information to be included.

Manufacture of active ingredient/s of the proposed new registered complementary medicine

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

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.

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

Control of active ingredients

The standards recognised under the *Therapeutic Goods Act 1989* (the Act) are those made by the Minister under Section 10 of the Act (Therapeutic Goods Orders) and the default standards, which currently are relevant statements in monographs in any of the following: *British Pharmacopoeia* (BP), *European Pharmacopoeia* (Ph. Eur.) or the *United States Pharmacopeia – National Formulary* (USP). It should be noted that any matter specified in an order under section 10 of the Act has precedence over requirements of the default standards.

The general monographs of the BP, Ph. Eur. and USP are also relevant, for example: the BP monographs 'Herbal Drugs', 'Herbal Drug Preparations' and 'Extracts'.

The most recent edition of the cited pharmacopoeia should be used.

Under current Australian legislation, if an ingredient is subject to a specific monograph in the BP, USP or the Ph. Eur, it must comply with the requirements of that monograph. If the ingredient is subject to more than one monograph, the manufacturer may nominate which will be adopted. 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

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 EMEA guidelines:

- Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances

- Guideline on specifications: Test procedures and acceptance criteria for herbal substances, herbal preparations and herbal medicinal products/ traditional herbal medicinal products

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; or
- adopt an earlier edition of the pharmacopoeial monograph or standard.

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.

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.

Impurities and incidental constituents

For guidance on this matter, refer to ARGCM Attachment 1 'Compositional guidelines: 'impurities and Incidental Constituents'.

For solvent impurities refer to the ICH document Impurities: guideline for residual solvents.

Batch certificates of analysis

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/stability data have been provided. If certificates of analysis are not available, justification as to why they have not been supplied must be provided.

Container closure system

A brief description of the container closure system for the raw material should be included. The suitability should be discussed, particularly with respect to, for example, choice of materials, protection from moisture and light, compatibility with the materials of construction.

Stability data for active ingredients

[redacted] Previously this was required only for new actives.

Stability data should be provided for the 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 EMEA guideline: Guideline on stability testing: Stability testing of existing active substances and related finished products.

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Finished product

Description and composition of the product

A description of the finished product that includes the following information should be provided:

- table of the ingredients and their purpose in the formulation (for example: active, disintegrant, antimicrobial preservative)
- a visual description of the dosage form, including any special characteristics (for example: modified release);and
- type of container and closure, including materials.

The table of ingredients should use Australian approved name (AAN) terminology and should provide greater detail than simply the product formulation. It should include any overages (additional amounts of ingredients over the amounts nominated in the product's formulation, added during manufacture). The table should also include a reference to the quality standard for each of the ingredients (for example: pharmacopoeial monograph reference or manufacturer's specifications number).

Medicine 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.

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.

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.

Formulation details for the medicine

The application should include a table of all the ingredients in the product which includes:

- their purpose in the formulation (for example: active, disintegrant, antimicrobial preservative). Each excipient ingredient included in a formulation must have a justifiable excipient role and be used in appropriate amounts to achieve its technical purpose
- 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); and
- a reference to the quality standard for each of the ingredients, for example: a pharmacopoeial monograph reference or manufacturer's specifications number.

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Batch to batch variations in the amount of active ingredients

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.

Batch to batch variations in the amount of excipients

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 1 lists the changes to the nominal amounts of certain excipients that may be made in the manufacture of immediate release registered complementary medicines.

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Table 1 Allowed changes to the nominal amounts of certain excipients

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 (e.g. magnesium stearate,)	+/– 25%
Filler (bulking agent) in hard gelatin capsules	+/– 10%
Polishing agents	qs
Carriers and potency-adjusting ingredients for materials of biological,herbal origin	+/– 10%
Filler (bulking agent) in tablets and soft gelatin 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'

Manufacture of the medicine

Licensing and control

All medicines must be manufactured in accordance with the principles of good manufacturing practice.

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Australian manufacturers

Australian manufacturers must comply with the PIC/S Guide to Good Manufacturing Practice for Medicinal Products. The manufacturer of each step in the manufacture of the medicine must be licensed to perform that step.

Overseas manufacturers

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

- GMP clearance for overseas manufacturers and
- Questions & answers on the code of good manufacturing practice for medicinal products.

Description of manufacturing process

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:

- overages
- solvents that are used, even if they are evaporated from the medicine during manufacture; and
- 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).

Control of ingredients

Control of excipients

Where applicable, excipient ingredients subject to a specific monograph in the BP, USP or Ph. Eur. 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.

Control of proprietary ingredients

The specifications applied to proprietary ingredients should be appropriate for the nature of the ingredient, and for its function and proportion in the finished product. For an active premix that contains the active ingredient, specifications must include tests for the identification and content of the active ingredient and impurity tests.

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Control of colouring ingredients

Colours permitted in oral medicines are specified in the document 'Colourings permitted in medicines for oral use' is available on the TGA website. 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.

Control of the finished product- specifications

The finished product specifications should be provided. The finished product specification is the set of tests and limits that are applied to the finished medicinal product in order to ensure that every batch is of satisfactory and consistent quality at release and throughout its shelf life. The specifications should include all critical parameters in which variations would be likely to affect the safety or efficacy of the product, for example: assay. The specifications' code numbers and date should also be specified.

The specification should include both the batch release and expiry specifications should be included. 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. For example, if the batch release and expiry limits for assay are identical, the implication is that there will be no loss of the active ingredient throughout the shelf life.

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 another, appropriately validated, method.

Useful guidance on the development of product specifications is provided in the following ICH documents:

- Specifications: Test procedures and acceptance criteria for new drug substances and new drug products: Chemical substances

For demonstration of quality for herbal complementary medicines, the following ICH documents provide useful guidance:

- Guideline on quality of herbal medicinal products/ traditional herbal medicinal products 31st March 2011.
- Guideline on Specifications: test procedures and acceptance criteria for herbal substances, herbal preparations and herbal medicinal products/ traditional herbal medicinal products 31st March 2011.
- Guideline on quality of combination herbal medicinal products/ traditional herbal medicinal products November 2008

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

The general monographs of the BP, 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.

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), a consent to supply the product is required (refer to ARGCM Part B 'Consent to supply goods that are not compliant with certain legislative requirements').

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.

Solvent residues

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.

Impurity requirements for 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 ICH guideline on impurities in new drug products.

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. 77 - Microbiological Standards for Medicines (TGO 77) 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

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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.

Analytical procedures & validation

Details of analytical methods should be provided for all tests proposed in the specifications. Stability –indicating, where applicable, and appropriately validated methods should be used. Details of the analytical method validation should also be provided in the dossier.

Batch certificates of analysis

The applicant 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, the applicant 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.

Container

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 product and its performance in protecting the product physically and also in protecting it from 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.

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Measuring devices or other dose delivery devices

Some measuring devices or dose delivering devices may require a separate listing on the ARTG, sponsors should refer to the Australian Regulatory Guidelines for Medical Devices (ARGMD) for further guidance.

All submissions should include details of any measuring device or other dose delivery device that is intended to be supplied with an OTC medicine. The submission should include a copy of the specifications for the measuring device. If the design, composition and performance of the device is not clearly described in the submitted specifications, it may be necessary to submit drawings or a sample of the measuring device for evaluation.

Calibrations on measuring devices should be exclusively in metric units and allow all the doses shown on the labels to be measured accurately.

The ability of the device to deliver the correct dose accurately and reproducibly must be ensured. In particular, the BP/Ph. Eur. Appendix XII C. Consistency of Formulated Preparations includes a test and requirement for Uniformity of Weight (Mass) of Delivered Doses from Multidose Containers (Ph. Eur. monograph 2.9.27). Where this requirement applies, it is sufficient that the sponsor provide an assurance that the proposed measuring device complies with the requirements of this test.

Child resistant closures

TGO No. 80 – Child-Resistant Packaging Requirements for Medicines (TGO 80) specifies requirements relating to the use of child-resistant packaging (CRP) for medicines which 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.

Finished product stability

The stability data must be sufficient to demonstrate, or indicate with a high probability, that the product intended for market will remain safe, of consistent quality and efficacious

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throughout the product's shelf life. The stability data will form the basis for setting a shelf life and recommended storage conditions for the product. Refer to the ICH guideline on: Stability testing of existing active substances and related finished products.

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 – 15 January 2009).

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 three 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 product's registration.

Stability protocol for self-assessable shelf life extension

A product'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 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')
- a statement of the criteria for notifying a shelf-life increase (e.g. 'Full-term stability data will be generated using two production batches stored at y C. All analytical results obtained will comply with the protocol acceptance criteria; otherwise, the TGA will be notified immediately')
- the precise formulation of the product (if overages are included, this should be stated and a justification provided)

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- 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); and
- 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 product 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 product (other than as specified in the notification) have been made, or are currently proposed to be made
- a stability testing protocol has been approved for the product and a copy of the approval letter is attached to the notification
- at least two full production batches of the Australian formulation product packed in the approved container have been used in the studies; and
- 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; and
- 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.

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Attachment 18A: Changes to registered complementary medicines

[redacted] Why don't the same rules, timelines and change codes apply to registered CMs as to registered OTCs?

Consideration of a proposed change to a registered complementary medicine

In specific circumstances, as outlined in Attachment 18B, some minor changes to a registered complementary medicine are not required to be notified to the TGA, for example: additional analytical tests or tightening of product specifications.

There are also provisions in the legislation for certain details to be amended on a medicines' Australian Register of Therapeutic Goods (ARTG) entry, upon request by the sponsor, and maintain the same AUST R number.

All applications for changes to registered complementary medicines attract an application fee. For certain applications a separate evaluation fee is also payable. Information on current fees is available on the TGA website. Regulation 45 of the Therapeutic Goods Regulations 1990 (the Regulations) provides for the waiver or reduction of evaluation fees under certain circumstances.

The following information provides guidance for a sponsor to consider when proposing a change to a registered complementary medicine.

Would the proposed change to the medicine create a new medicine (a 'separate and distinct' good)?

Section 16(1) of the *Therapeutic Goods Act 1989* (the Act) outlines those criteria which make registered medicines separate and distinct from the existing goods:

> For the purposes of this Part, therapeutic goods (other than medicine of the kind to which subsection (1A) applies) are to be taken to be separate and distinct from other therapeutic goods if they have:
> (a) a different formulation, composition or design specification; or
> (b) a different strength or size (disregarding pack size); or
> (c) a different dosage form or model; or
> (d) a different name; or
> (e) different indications; or
> (f) different directions for use; or
> (g) a different type of container (disregarding container size).

Where the proposed change will result in a good considered 'separate and distinct' from the existing good, applicants will need to submit a new application for registration of the medicine, which may result in a new AUST R number.

However, note that:

- where the new medicine is intended to replace the currently supplied medicine, the new medicine may meet the criteria to be 'grouped' under the ARTG entry of the existing medicine and be assigned the same AUST R number (see below); or
- if the change is to an indication (which technically would make the medicine 'separate and distinct'), but the change only reduces the class of persons for whom the goods are suitable, a variation to the existing medicine under section 9D 2 of the Act may be possible (see below).

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Is the proposed change of a type permitted under section 9D of the Act?

Section 9D (1), (2) and (3) of the Act provides the circumstances under which a sponsor may request an amendment to the ARTG entry for their registered medicine and maintain the same AUST R number.

> 9D Variation of entries in Register
> (1) The Secretary may:
> (a) following a request by a person in relation to whom therapeutic goods are entered on the Register; or
> (b) on the Secretary's own initiative;
> vary the entry in the Register in relation to the goods if the entry contains information that is incomplete or incorrect.
> (2) If:
> (a) the person in relation to whom therapeutic goods are registered or listed has requested the Secretary to vary information included in the entry in the Register that relates to the goods; and
> (b) the only effect of the variation would be:
> (i) to reduce the class of persons for whom the goods are suitable; or
> (ii) to add a warning, or precaution, that does not include any comparison of the goods with any other therapeutic goods by reference to quality, safety or efficacy;
> the Secretary must vary the entry in accordance with the request.
> (2A) Subsection (2), to the extent to which it relates to subparagraph (2)(b)(i), applies despite subsection 16(1).
> (3) If:
> (a) the person in relation to whom therapeutic goods are registered or listed has requested the Secretary to vary information included in the entry in the Register that relates to the goods; and
> (b) subsection (2) does not apply to the request; and
> (c) the Secretary is satisfied that the variation requested does not indicate any reduction in the quality, safety or efficacy of the goods for the purposes for which they are to be used;
> the Secretary may vary the entry in accordance with the request.

Briefly, the provisions under section 9D include:

- section 9D(1) provides for correction of an ARTG entry of a medicine that is incomplete or incorrect
- section 9D(2) provides for making certain safety-related variations to an ARTG entry of a medicine. A variation is safety-related if it reduces the patient population (such as by removing an indication), or has the effect of adding a warning or precaution (such as an adverse effect or interaction); and
- section 9D(3) provides for other variations to an ARTG entry of a medicine to be made, provided that the Delegate of the Secretary is satisfied that the change does not reduce the quality, safety or efficacy of the medicine.

Attachment 18B provides a list ('Changes tables') of possible changes to registered complementary medicines and indicates the applicable fees and the type of assurances or data required to support the application. Note that, if a description of the proposed change cannot be found in the Changes Tables, you should contact the TGA - the absence of the proposed change does not imply that you may proceed with the change without notifying the TGA.

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Would the proposed change meet the criteria for grouping as provided in The Therapeutic Goods (Groups) Order?

The Therapeutic Goods (Groups) Order No. 1 of 2001 (Groups Order) provides the criteria whereby a 'new' medicine can be 'grouped' under the existing medicine's ARTG entry and be assigned the same AUST R number. A grouping is appropriate where the new medicine is intended to replace the existing medicine, enabling the transition from one medicine to another. However, individual products within the group remain separate and distinct products under section 16(1) and (1A) of the Act.

Briefly, under the Groups Order, therapeutic goods may be grouped under one ARTG entry when the new product is to replace the existing one (or be registered in place of the existing medicine) and the only change is one of the following:

[redacted] We note that the ARGOM provides change codes for changes under the Groups Order. We question why these cannot be provided for registered CMs.

- name change; or
- increasing or decreasing the amount of an excipient (but not the addition or deletion of an excipient); or
- removal or addition of a fragrance, flavour, printing ink or colour; or
- revised indications and/or directions for use.

Chart 1 provides an overview of avenues for changing information for a registered complementary medicine. This diagram is provided as general guidance and is not comprehensive. Sponsors should contact the TGA for specific questions relating to possible changes to their medicine. Section 16(1) and (1A) of the Act list the differences that will result in goods being considered separate and distinct from other goods.

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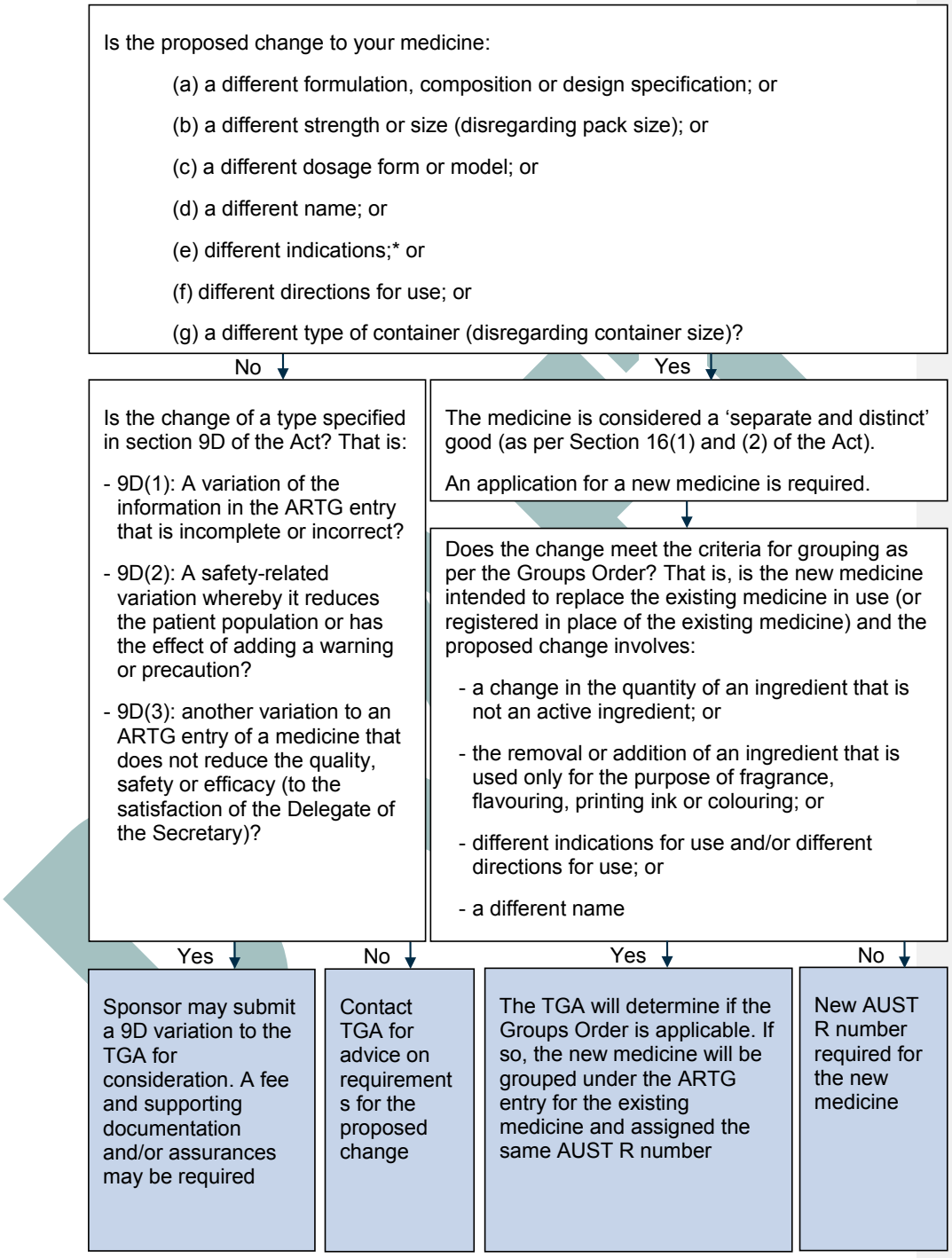
Chart 1: Changing ARTG information for registered complementary medicines



*Note: If the proposed change to the medicine indication is only to reduce the patient population, a variation application under section 9D(2) of the Act may be possible. Contact the TGA.

Process for applying for a variation to a registered complementary medicine under section 9D of the Act.

An application for variation of a medicine should be submitted on the Registered medicine variation form (complementary medicines). If approved, the change to the ARTG entry is made by the TGA and the AUST R number is retained

How will the TGA acknowledge my application for a 9D variation?

Sponsors will be sent an acknowledgment in response to their application. For approved changes, a letter of approval, signed by the Delegate of the Secretary (the Delegate) is sent. Should the application be refused, a rejection letter containing reasons for the decision and details of procedures for review of the decision will be sent.

What else do I need to send to support my application for a 9D variation?

For most applications sponsors will need to submit supporting documentation with the variation application form, for example: if sponsors wish to change details of the label, they will need to send a copy of the present label and a draft copy of the new label. In some instances, certain assurances about the change will also need to be made before the application can proceed – refer to the Changes Tables in Attachment 18B.

Will the TGA look at other aspects of the medicine that are not being changed?

Generally, the TGA will only review the requested change at the time of the variation application. However, some changes affect other aspects of the medicine, which may require further clarification, for example: a manufacturing process change may also require change to finished product specifications. Sponsors can minimise the potential for delays by ensuring the medicine complies with all current legislative requirements.

Can I make the same changes for many products under the 9D variation application?

If sponsors wish to implement an identical change, that does not attract an evaluation fee, across a range of similar products, only one application form may need to be completed in certain cases. An example is the notification of a change of the same manufacturer (licensed) for a range of registered products. However, a significant change to several products (for example: changes to the recommended storage conditions) would require individual applications for each product.

Process for applying for a new medicine that may meet the criteria for a gazetted therapeutic goods group

If it is considered that the proposed change would meet the criteria of the Groups Order, the sponsor can submit an registered medicine application- grouped medicines. If approved by the Delegate, the new medicine is 'grouped' in the ARTG under the same AUST R number.

How will the TGA acknowledge my application for a new medicine that may meet the criteria for a gazetted therapeutic goods group?

Sponsors will be sent an acknowledgment letter in response to their application. If the application is approved, a letter of approval, signed by the Delegate, will be provided. Should the application be refused, a rejection letter containing reasons for the decision and details of procedures for review of the decision will be provided.

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Attachment 18B: Changes tables for registered complementary medicines

Tables 4 to 13 (the 'Changes tables') list the types of changes to a registered complementary medicine that may be permitted under section 9D of the *Therapeutic Goods Act 1989* (the Act). Tables 1 to 3 provide the codes (for the application type, the required documentation and the types of assurances required) used in the Changes tables.

[redacted] See ARGOM Guidelines on Changes to OTC Medicines v 1.1, April 2013, pp 11 to 32.

These tables assist clarity of requirements e.g. when something is new, and when it can be grouped.

Note that the status NEW is provided.

The requirement to ASK for grouping advice will be reduced, lessening the burden on OCM and sponsors.

Note that if a sponsor cannot find a description of the proposed change for their medicine in the Changes tables, you should contact the TGA. The absence of the proposed change does not imply that you may proceed with the change without notifying the TGA.

Table 1 'Application type' codes used in changes tables (tables 4 to 13)

Codes for application type (as used in tables 4 to 13)	
Code	**Meaning**
A	Approval required. Application - Evaluation fee is payable.
N	Notification required. Application - No ~~evaluation~~ evaluation fee is payable.
O	No application required. Changes with status 'O' have been included for completeness.
NEW	New Application for registration required.
ASK	Contact the TGA

Table 2: 'Required documentation' codes used in changes tables (tables 4 to 13)

Codes for required documentation (as used in tables 4 to 13)	
Code	**Meaning**
E	Evidence to support the change where an ARTG entry is to be corrected.
L	A copy of the current label of the goods plus a draft copy of the new label, with the relevant changes highlighted, have been supplied. If the medicine has a package insert, CMI and/or a PI, these documents (current and draft) should also be supplied when the change impacts on them.
PI	A copy of the current Product Information (PI) of the product plus a draft copy of the new PI, with the relevant changes highlighted, have been supplied.

Codes for required documentation (as used in tables 4 to 13)	
Code	**Meaning**
P	The Poisons Standard schedule (or 'N' for unscheduled goods) for the new pack size is stated in the application form.
1.	The 'new' goods are intended to replace the existing goods in use.

Table 3: 'Types of assurances required' codes used in changes tables (tables 4 to 13)

Codes for types of assurances required in support of the application (as used in tables 4 to 13)	
Code	**Meaning**
1.	No additional indications have been introduced or directions for use altered (other than change to wording).
2.	No aspects of the labelling, PI, CMI, pharmaceutical data or other product details have been changed or are to be changed, other than changes nominated in this application and those made in conformity with the Changes Table.
3.	The labelling for the new pack size is unchanged, other than to indicate the new pack size number/volume.
4.	The only changes made are those that bring the label into compliance with requirements of the Labelling Order, or Schedule 2 to the Therapeutic Goods Regulations 1990.
5.	The change is in compliance with a requirement introduced in the most recent version or amendment of the Standard for the Uniform Scheduling of Medicines and Poisons or Required Advisory Statements for Medicine Labels.
6.	The nominated manufacturer is licensed to manufacture products of this type.
7.	The container type (as defined in TGA Approved Terminology for Drugs) is unchanged and container material is unchanged.
8.	A stability testing protocol has been approved for this product and a copy of the approval letter is attached.

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Codes for types of assurances required in support of the application (as used in tables 4 to 13)	
Code	**Meaning**
9.	All of the following: neither the existing nor the new material is a modified starch the changeover has been validated at least 6 months stability data have been generated at the maximum recommended storage temperature on product manufactured using the new type of starch, or 3 months data at a temperature at least 10°C higher than the maximum recommended storage temperature stability testing will continue for the full term of the product's shelf life, any batches not meeting specifications will be withdrawn from the market immediately, and the OCM will be notified immediately.
10.	The changeover has been validated and the sponsor is satisfied that the change will not adversely affect the stability of the product. Stability testing will continue for the full term of the product's shelf life and the TGA will be advised immediately of any batches not meeting specifications.
11.	No new text or graphics have been introduced.
12.	The change of material is one of the following: polystyrene to PVC, polyethylene, polypropylene or glass PVC to polyethylene, polypropylene or glass polyethylene to glass or polypropylene of density ≥ 0.89 from one density of polyethylene to a higher density any change between glass, polyethylene of density ≥ 0.95, and polypropylene of density ≥ 0.89.
13.	The new container/closure system has demonstrated equal or better moisture protection in the USP Test for Containers – Permeation (water vapour transmission) to that of the existing container/closure system.
14.	The information on the container label is not less than the information on the primary pack.
15.	The change to the plastic component is one of the following: PVC to PVC/PVDC or to PVC/PCTFE PVC/PVDC to PVC/PCTFE; or the change to the plastic component is to a material with demonstrated lower or equivalent water permeability than the existing material (see for example USP monograph 671 Containers Permeation).

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Codes for types of assurances required in support of the application (as used in tables 4 to 13)	
Code	**Meaning**
16.	Manufacturing method and specifications, other than visual identification, have not been changed.
17.	Two production batches have been tested according to the approved stability protocol and all results fall within the acceptance criteria, as specified in the approved stability protocol.
18.	The changes are in accordance with s.9D(1) of the Therapeutic Goods Act 1989.

Table 4: Label changes table (including package insert/CMI)

[redacted] Why have the NEW, GPN, GPU, GIN, and GID been removed?
See pp 14-17 of 32 of the ARGOM changes tables.

Code	Label change	Status	Assurances/ Documentation	Legislative basis
LIW	Therapeutic indications or directions for use – change of wording without altering meaning	A	1, L	9D(3)
LIS	Therapeutic indications – removal of subset of indications from label	N	2, L	9D(2)
LIR	Therapeutic indications – addition of registered indications to label	A	2, L	9D(3)
GDU	Directions for use – e.g. dosage instructions – change of wording without altering meaning.	A	L	9D(3)
GDD	Directions for use—e.g. dosage instructions (if grouping applies) where supporting data or a justification for not providing supporting data is required. (See also LIW)	A	1, 3, L	23
PSC	Recommended storage conditions – more restrictive	N	2, L	9D(3)
PST	Recommended storage conditions – less restrictive	A	2, L	9D(3)
LSR	Addition of more restrictive safety-related statements	N	2, L	9D(2)

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Code	Label change	Status	Assurances/ Documentation	Legislative basis
LSF	Changes on label (signal headings, warning statements) in compliance with new Poisons Standard requirements, where there is a change in scheduling	A	2, L	9D(2)/ 9D(3)
LSU	Changes on label (signal headings, warning statements) in compliance with new the Poisons Standard requirements, other than LSF	N	2, 5, L	9D(2)/ 9D(3)
LLO	Changes to bring a label into compliance with the Labelling Order – other than changes to the proprietary name, indications or directions for use	N	2, 4, L	9D(2)/ 9D(3)
LLR	Addition of a required representation to a label (Schedule 2 to the Therapeutic Goods Regulations)	N	2, 4, L	9D(2)
LCF	Colour, font, type size only (no change in label copy)	N	2, L	9D(3)
LGR	Introduction of new graphics/icons (other than as specified in change SSP or KSP)	A	2, L	9D(3)
RGR	Removal of a graphic (other than as specified in change SSP)	N	5, L	9D(1)/ 9D(3)
LFO	Reformatting of pre-existing text (i.e. moving of blocks of text and not rewording – see LIW, LRT)	N	2, L	9D(3)
LRT	Rewording of pre-existing text without altering meaning (other than indications or directions for use – see LIW)	A	L	9D(3)
LDT	Deletion or addition of text to the label (e.g. addition or removal of claims such as clinically proven, fast/rapid action; general claims regarding the product, its nature, mechanism of action, qualifying statements etc)	A	L	9D(3)
LOC	Other changes	ASK	-	
COO	Addition or deletion of a country of origin statement e.g. 'Made in xx'	N	5, L	9D(3)

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Table 5: Sponsor changes table

Code	Sponsor change	Status	Assurances/ Documentation	Legislative basis
SSP	Sponsor name/logo/ sponsor address (same sponsor of goods) and/or change to manufacturer/supplier details on label	N	2, L	9D(3)

Table 6: Product details changes table

[redacted] See pp 20-22 of ARGOM.

Code	Product detail change	Status	Assurances/ Documentation	Legislative basis
PSZ	Pack size – other than liquids/semi-solids (see PLS) or metered dose aerosols (see PMZ) (see also KBT, KGL, KBL and KOT)	N	2, 3, 7, L, P	9D(3)
PLS	Pack size – liquids/semi-solids	N	2, 3, 7, 10, L, P	9D(3)
PMZ	Pack size – metered dose aerosols	A	-	9D(3)
PVI	Visual identification (note that novelty shapes, e.g. animal-shaped tablets, are not acceptable)	N	2, 10, 16	9D(3)
PSL	Shelf life – increase (other than in change PSP)	A	-	9D(3)
PSR	Shelf life – decrease	N	2	9D(3)
PSP	Shelf life – increase (in accordance with an approved stability testing protocol for that product)	N	2, 8, 17	9D(3)
PPR	Approval of a stability testing protocol for a specific product	A	-	9D(3)
PSC	Recommended storage conditions – more restrictive	N	2, L	9D(3)
PST	Recommended storage conditions – less restrictive	A	2, L	9D(3)

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Code	Product detail change	Status	Assurances/ Documentation	Legislative basis
PMI	Sterility status/technique	A	-	9D(3)

Table 7: Quality control changes – finished product specifications changes table

Code	Finished product specification change	Status	Assurances/ Documentation	Legislative basis
QFX	Specification ranges – more restrictive	O	-	
QFE	Specification ranges – less restrictive [This might result in a making the goods separate and distinct under S16(1)].	A	-	9D(3)
QFT	Addition of an extra test	O	-	
QFU	Deletion of an existing test	A	-	9D(3)
QFA	Analytical method – to comply with amendments to a standard (e.g. the BP, Ph Eur, USP or a TGO)	O	-	
QFB	Analytical method – which has been demonstrated to maintain or improve analytical performance (accuracy, precision and/or specificity)	ASK	-	
QFC	Analytical method – other than as specified above in change QFB	A	-	9D(3)
QFS	Expiry specification ranges following changes to the BP, Ph Eur, USP or the *General standard for tablets, pills and capsules or changes to USP where a USP monograph has been approved by the TGA in relation to the product*	O	-	

[redacted] This is O in OTC requirements.

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Table 8: Quality control changes – starting material specifications changes table

Code	Starting material specification change	Status	Assurances/ Documentation	Legislative basis
QSX	Range – more restrictive	O	-	
QSE	Range – less restrictive [This might result in a making the goods separate and distinct under S16(1)].	A	-	9D(3)
QST	Addition of an extra test	O	-	
QSU	Deletion of an existing test	A	-	9D(3)
QSA	Analytical method – to comply with amendments to a standard (e.g. the BP, Ph Eur, USP or a TGO)	O	-	
QSB	Analytical method – which has been demonstrated to maintain or improve analytical performance (accuracy, precision and/or specificity)	ASK	-	
QSC	Analytical method – other than as specified above in change QSB	A	-	9D(3)
QSM	Manufacturer of starting material (specifications unchanged)	O	-	
QSS	Supplier of starting material	O	-	

[redacted] This is O in OTC.

Table 9: Packaging changes table

Code	Packaging change	Status	Assurances/ Documentation	Legislative basis
KBT	Container material – if the container is a bottle, the goods are a solid dosage form (e.g. tablet) and the change is of a type listed in assurance 15 [note that this might result in a making the goods separate and distinct under S16(1)(g)].	N	2, 7, 10, 12 & 13	9D(3)
KGL	Container material – clear to coloured glass	N	2, 7, 10, 12 & 13	9D(3)

[redacted] This is O in OTC.

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Code	Packaging change	Status	Assurances/ Documentation	Legislative basis
KBL	Container material – if the container is a blister pack, the goods are a solid dosage form (e.g. tablet) and the change is of a type listed in assurance 15	N	2, 7, 10 & 15 5, 10, 13 & 8	9D(3)
KOT	Container material – other than in changes KBT, KGL or KBL [This might result in a making the goods separate and distinct under S16(1)(g)]	A	-	9D(3)
KCL	Closure	N	2, 10 5, 13	9D(3)
KSL	Tamper-resistant seal – addition (including label notice to alert consumers to presence of seal)	O	-	
KSX	Tamper-resistant seal – removal (including removal of label notice re seal)	O	-	
KWA	Inert wadding material – addition, substitution or removal where stability is not affected by the action	O	-	
KDA	Desiccant – inclusion in container	A	-	9D(3)
KDX	Desiccant – removal from container	A	-	9D(3)
KPP	Specifications of primary pack (other than labelling)	O	-	
KSP	Introduction of a measuring device (e.g. spoon, cylinder) or applicator (e.g. finger cot); this change can include graphical representation of the device on the label (copy of current and proposed label must be supplied if label is changed)	N	2, L	9D(3)
KMD	Changes to existing measuring device (e.g. spoon, cylinder) or applicator supplied with the goods, or removal of a measuring device or applicator, where other means of accurately measuring or applying the dose are readily available	N	2, L 5	9D(3)
KPA	Introduction of a primary pack (no new text or graphics)	N	2, 11	9D(3)

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Code	Packaging change	Status	Assurances/ Documentation	Legislative basis
KPI	Introduction of a package insert	A	L	9D(3)
KRI	Removal of a package insert	A	L	9D(3)
	Changes to package insert (see Label Change section)		-	
KPX	Removal of a primary pack	N	2, 14	9D(3)
KRP	Introduction of a refill pack [This might result in a making the goods separate and distinct under S16(1)(g)]	A	-	9D(3)
KRR	Removal of refill pack [This might result in a making the goods separate and distinct under S16(1)(g)]	N	-	9D(3)
MDA	Changes in pump or pump components of meter-dose aerosol (e.g. valve material)	A		9D(3)

Table 10: Manufacturing changes – finished product changes table

Code	Manufacturing change	Status	Assurances/ Documentation	Legislative basis
MMA	Addition or deletion of TGA-licensed Australian manufacturer (includes site of manufacture)	N	2, 6	9D(3)
MOS	Addition or deletion of overseas manufacturer (includes site of manufacture)	N	2, 6	9D(3)
MPR	Manufacturing process (other than MBS)	N	10	9D(3)
MBS	Batch size for pressurised inhalation (nasal and oral respiratory) products	A	-	9D(3)
AMS	Addition or deletion of steps of manufacture of a TGA licensed Australian manufacturer	N	5, 9	9D(3)
OMS	Addition or deletion of steps of manufacture of an overseas manufacturer	N	5, 9	9D(3)

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Code	Manufacturing change	Status	Assurances/ Documentation	Legislative basis
MUP	GMP clearance NUMBER update. Note: no other change to record permitted under this code. If amending steps of manufacture use change code OMS	N	Fee exempt 5	9D (3)
MST	Change to manufacturing site and/or process of sterile product	A		9D(3)

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Table 11: Consumer Medicine Information (CMI) changes table

Code	CMI change	Status	Assurances/ Documentation	Legislative basis
CPI	Introduction of a CMI for a 'Pharmacist Only Medicine' (Schedule 3) product registered after 4 July 1995 where the CMI complies with Schedule 13 to the Therapeutic Goods Regulations and is not to be included as a package insert*.	O		
CPO	Changes to an existing CMI, where the changes are consistent with all previously approved product details and the CMI is not to be included as a package insert. **	O		
* Note: Change KPI applies where the CMI is to be included as a package insert. ** Note: Refer to the Label Change section for guidance on changes to a CMI where the CMI is to be supplied directly with the medicine (a CMI is treated as part of the label when it is on or attached to the goods; or on or attached to a container or primary pack in which the goods are supplied; or supplied with such a container or pack).				

Table 12: Product Information (PI) changes table

Code	Change	Status	Assurances/ Documentation	Legislative basis
DPI	Introduction of a PI for an existing product.	A	-	9D(3)
DRS	Addition of more restrictive safety-related statements.	N	2, PI	9D(2)
DOT	Changes other than the addition of more restrictive safety-related statements.	A	-	9D(3)

Table 13: Other changes table

Code	Change	Status	Assurances/ Documentation	Legislative basis
CTA	Correction of ARTG record in accordance with section 9D(1) of the Therapeutic Goods Act 1989	N	E, 2, 17	9D(1)

[redacted] No BED, BES or OTH?

DRAFT

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