Operations	Office of Complementary Medicines
Procedure	Generation and Maintenance of Compositional Guidelines for Listed Medicine Substances
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Authorised by:	
Date Issued	
Revision #	0

1. Aim/Purpose/Scope

This SOP details the process to be followed when developing a Compositional Guideline for a listed medicine substance, commencing with the receipt of a draft guideline from an applicant to presenting the final version on the TGA website.

2. Responsibility

This SOP is prepared and maintained by the relevant officer (Compositional Guidelines Officer) within OCM charged with this task.

3. Introduction/Background

Compositional Guidelines are provided on the TGA website to assist sponsors in sourcing materials for listed medicines which do not have a monograph in a recognised pharmacopeia (BP, EP, USP). They provide the definition, specifications and appropriate test methods (none of which are currently legally enforceable) that the substance is expected to comply with.

4. Policy/Procedure

1) Upon receipt of a draft CG from an applicant (a template is provided on the TGA website), the relevant officer should generate a TRIM file for the guideline with an accompanying modifications log.

2) The officer then confirms that no monograph exists in the BP, EP or USP. The officer screens the guideline for the following criteria:

i. The material has a satisfactory AAN/AHN/ABN
ii. The substance is satisfactorily defined with respect to it's origin and method of manufacture
iii. It meets the requirements of any pharmacopeial standards applicable to substance types (e.g. BP guideline for herbal substances).
iv. The substance has an adequate identification test
v. The substance has an adequate assay test and method
vi. The substance has an adequate suite of characterisation specifications

vii. The substance has adequate limits and methods for incidentals such as heavy metals, solvents, pesticides.

viii. The limits are broadly consistent with other similar substances that do have pharmacopeial monographs

ix. The microbial limits either reference TGO 77 or are consistent with this order.

3) The CG officer informs the applicant of any deficiencies from the above criteria and amends the guideline in agreement with the applicant.

4) The agreed guideline is given to the communications liaison officer in OCM to be uploaded as a draft guideline. The guideline is presented as a draft and open for comment for a period of not more than six months (less if considered appropriate). During this time stakeholders may advise in writing of comments for the draft guideline.

5) Upon completion of the comment period, the guideline is labelled on the website as 'draft – closed for comment'. At this time the CG officer collates any comments received for the guideline (*via* the mailbox TGA.Comp.Guidelines@tga.gov.au) and assesses (with internal consultation with relevant experts where appropriate – see Compositional Guideline Meetings below). Any modifications made to the guideline are to be logged on the modifications page which accompanies the guideline in the relevant TRIM file.

6) If the changes to the draft guideline are minor (typographical corrections, changes to units etc) or none at all, the guideline may be modified then presented as a final guideline on the website. If the changes are substantial (eg alteration of limits, change in the allowable manufacture) the modified guideline may be re-posted as a draft for further comment with a closing date for submissions.

7) A 'finalised' guideline should not be considered inalterable and comments on such guidelines should be considered as appropriate.

8) Additionally, it may be necessary to modify a finalised guideline to comply with new TGOs or update method references. These modifications should be preformed at the earliest convenient time and noted on that guideline's modification log sheet.

Compositional Guideline Meetings

Once per month the compositional guidelines officer is to call a meeting with up to three other members of the OCM with relevant expertise to assess the comments and suggestions received or any draft compositional guidelines whose period for comment has expired since the previous meeting. The meetings are to serve as an expert advisory panel to evaluate any suggested modifications and determine whether they are justified. Any other matters of concern with other guidelines may also be discussed.

Discussion and resolution on any guideline is to be included on that guideline's modifications log.

5. References

TGO 77

ARGCM Part 3

Current versions of:

British Pharmacopeia

European Pharmacopeia

United States Pharmacopeia

6. Attachments

1 - Template for compositional guideline

2 - Template for modifications table

Draft Compositional Guideline for *XXXX*

Italicised text is for guidance only and should be removed prior to submission

Name of the ingredient

XXXX (*check the ARTG permitted ingredients list for the correct name and type of substance*)

Definition of the ingredient

The substance should be defined as to its origin (eg, genus, species, part of the organism, geographical location of harvest) and method of manufacture (cultivated or wild, extracted, dried, distilled purified by ion-exchange chromatography etc). This must be the same as the process against which the safety/toxicolgy data was evaluated by the TGA.

Molecular formula (*if applicable*):

CAS Number (*if applicable*):

Table 1. Ingredient specific requirements

Test	Method reference	Acceptance criteria
Description *This should include all physical properties which may be assessed without testing, such as appearance, odour, colour, particle size etc.*	*Where there is no formal testing regime required e.g. appearance or smell, a description such as 'organoleptic' or 'visual' is satisfactory*	*Criteria should be such that an incorrectly labelled substance could be identified as non-compliant*
Characteristics *Properties of the substance that ensure its quality. Pharmacopeial tests and limits for comparable substances should be considered when determining what to include. Some examples include:* Residue on ignition Sulfated ash Loss on drying Solubility Melting Point Peroxide Value pH of solution		*Limits should be declared as a percentage, e.g. < 1 % w/w.* *Ranges with more significant figures are preferable to single values with fewer significant figures, e.g. pH 3.5 – 4.5 is preferable to pH 4.*
Identification *The identification test must be able to unambiguously identify the substance from any other substance, especially related substances and may include 'fingerprint' tests such as tlc or FT-IR which must be compared to an authenticated reference material. For pure substances chromatographic retention time alone is generally considered inadequate as a method*		*E.g. Matches spectrum of authenticated reference material.*

Test	Method reference	Acceptance criteria
of identification.		
Assay *In the case of complex mixtures (eg herbal extracts) where the active(s) are unknown or cannot be assayed 'marker' compounds may be used as proxies. See EMEA 815/00..*	*Where the method is proprietary information, a statement of the type of method is adequate - details are not required for the guideline, but are expected in the application.*	*Ranges, not limits should be stated unless justified.*

Table 2. Incidental constituents

Certain incidentals tests may be excluded based on the origin and processing of the substance, e.g. a dried leaf, otherwise unprocessed, may be exempted from residual solvent testing. Other incidentals, such as PCBs, scheduled contaminants (e.g. bromides, ephedrine) or radioactivity should be included as appropriate.

Test	Method reference	Acceptance criteria
Solvent residues	*For example* *BP* (Vol IV, Appendix VIII L, Residual solvents; *Ph. Eur.* method 2.4.24)	complies
Incidental metals and non-metals *The four metals specified below should always be tested for. Other metals such as tin, copper, etc should be tested for if they are expected to be present in substantial quantities.*		
Total heavy metals	*BP* (Vol IV, Appendix VII Limit test for heavy metals; *Ph. Eur.* method 2.4.8) or in-house.	<5 ppm
Lead		<0.5 ppm
Arsenic		<0.5 ppm
Cadmium		<0.1 ppm
Mercury		<0.5 ppm
Copper		*Or otherwise justified*
Silicon		
Microbiology	The Therapeutic Goods Order No. 77 'Microbiological Standards for Medicines' mandates that any finished product which contains the ingredient, alone or in combination, must comply with the microbial acceptance criteria set by Clause 9 of the Order.	
Pesticide residues and environmental contaminants: (including agricultural and veterinary substances)	*BP* (Vol IV, Appendix XI L, Pesticide residues; *Ph. Eur.* method 2.8.13)	complies

Key to abbreviations: - insert any additional from above

AOAC = Association of Analytical Communities; *BP* = *British Pharmacopoeia* (currently promulgated edition), *Ph. Eur* = *European Pharmacopoeia*; *USP* = *United States Pharmacopoeia*; HPLC = high-pressure liquid chromatography; IR = infrared spectroscopy.

Compositional Guideline modification table

This table is to be linked with the relevant compositional guideline in TRIM

Substance:

Date	Action	By