Operations	Office of Complementary Medicines
Procedure	New substance application - screening process - technical
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1. Aim/Purpose/Scope

This SOP details the specific steps required to assess completeness of assessable information provided in data dossiers which have been received by the Office of Complementary Medicines (OCM) with an application to change details of product registration (change application). This SOP acts as an OCM internal policy instrument aimed at ensuring that all applications are processed in a similar and equitable way; it also provides a central point of reference where any changes in OCM policy can be detailed to technical staff.

2. Responsibility

The maintenance of the SOP is the responsibility of the Director of the OCM's Pre-Market Assessment Section (PREMAS).

The SOP applies to OCM's Pre-Market Assessment Section (PREMAS) technical staff undertaking preliminary assessment of data before the acceptance for full evaluation.

3. Introduction/Background

This SOP provides an outline of the technical checks required to be undertaken to assess the completeness of data dossiers received by the OCM's PREMAS in support of a new substance application. This SOP is not intended to provide exhaustive details of every aspect of the process and refers to other SOPs and assessment templates where necessary. The advice of the Principal Scientist (Director?) is to be sought if necessary.

Where a reference is made in this SOP to another OCM's PREMAS SOP, that SOP is the latest version found on the TGA's Intranet site.

4. Policy/Procedure

Applications for a new substance for use as an ingredient in complementary medicines are NOT made under the *Therapeutic Goods Act 1989* ('the Act'), but rather fall under individual contractual arrangements between the applicant and the TGA/OCM. It is important that powers granted under the Act are not quoted to substantiate any process and in decision making, except for the decision to approve the substance (via Listing Notice) which is made under subsection 9A(5) of the Act. However, there is no provision under the Act to reject the application for a new substance.

All new substance applications received by the OCM PREMAS undergo an administrative check in accordance with the OCM SOP *Processing Applications - APS 4 Admin Procedure.*

As part of the above process, it is determined if correct application and evaluation fees have been paid.

Following administrative processing, each application file and a full data dossier are given to the OCM's Principal Scientist (Director?) for screening before the application can be formally accepted for evaluation. The Principal Scientist (Director?) will formally assign (via PATS work database) the evaluator for screening.

Eligibility of a substance for use in listed complementary medicines

The following potential legislative barriers must be considered to determine if the proposed substance is eligible for use as an ingredient in listed complementary medicines.

Inclusion in the Food Standard Code

The definition of a therapeutic good in the Act specifically excludes goods (other than goods declared to be therapeutic goods under an order in force under section 7) for which there is a prescribed standard in the Australia New Zealand Food Standards Code as defined in subsection 3(1) of the *Australia New Zealand Food Authority Act 1991* (now defined in subsection 4(1) of the *Food Standards Australia New Zealand Act 1991*).

When a substance is captured by the Australia New Zealand Food Standards Code then, unless the TGA executive has determined that a declaration for it to be therapeutic good under an order in force under section 7 is warranted, the substance will be ineligible for use as an ingredient in listed complementary medicines, when that substance is a sole active ingredient.

Schedule 14 of the Regulations

If a substance is not considered to be complementary medicines substance, with respect Schedule 14 of the Regulations, the application should be referred for consideration to OTC/OPM. It is the responsibility of the Director of the PREMAS to direct the application to OPM or OTC for consideration. All responsibility for the processing and outcome of an application referred from the OCM is transferred with the application, unless other arrangements are agreed to. Given the diversity of complementary medicine ingredients described in Schedule 14 of the Regulations, a decision on the eligibility of a proposed substance will be considered on a case-by-case basis. The decision making process will consider the following criteria:

- claims of the substances against the description given in Schedule 14;
- the source of the substance;
- the concentration of the naturally occurring form of the substance;
- the degree of any refinement of the substance;
- the degree of physicochemical alteration of substance(s) from any unprocessed form; and
- the process by which the substance is derived.

The background to all decisions regarding the eligibility or ineligibility of a proposed substance against the criteria of Schedule 14 of the Regulations will be documented on file should detailed reference and discussion with the sponsor be required.

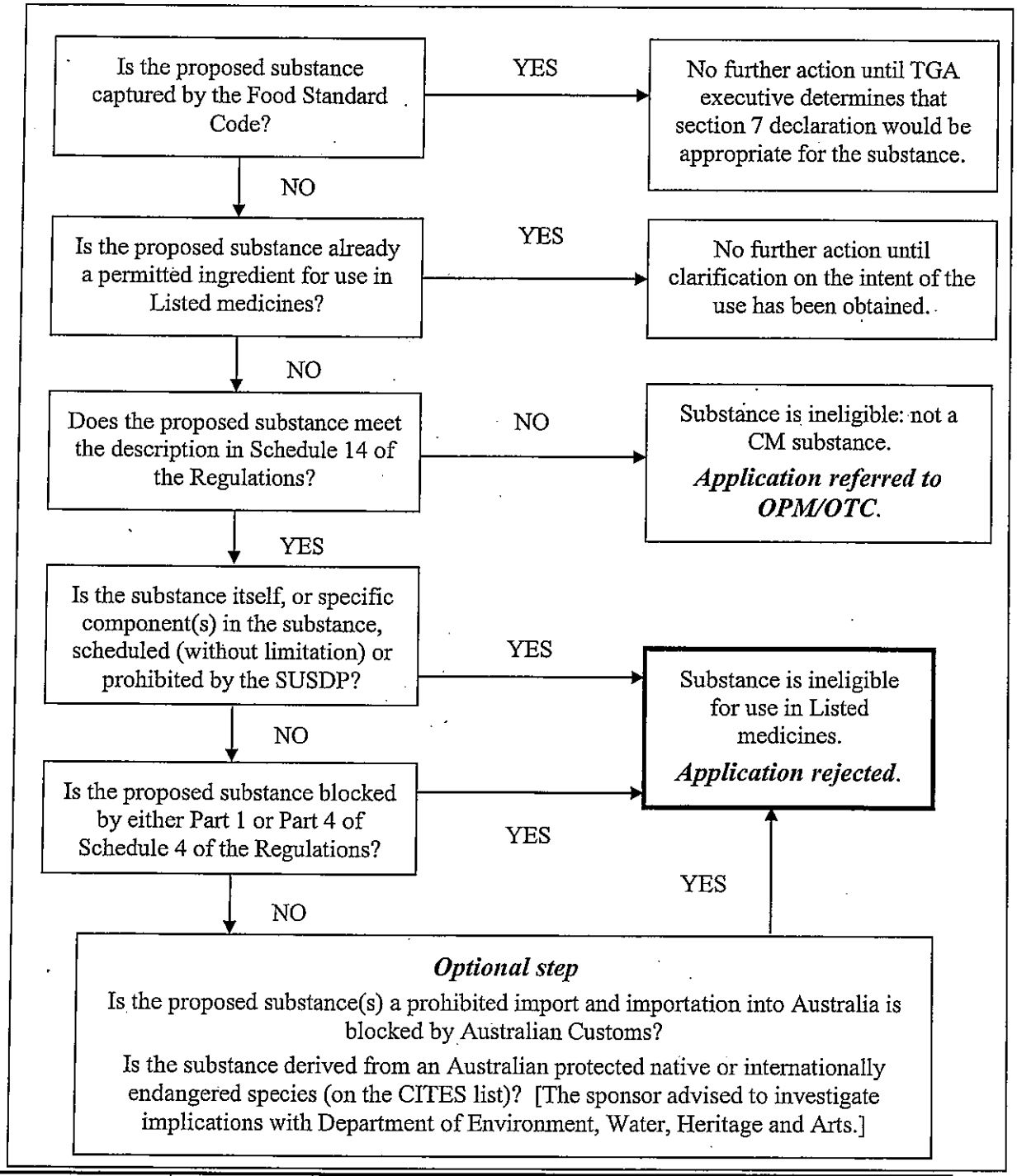
SUSDP scheduling

A proposed substance, which is cited in the SUSDP in the following manner cannot be used in listed medicines and is therefore ineligible for evaluation.

- Any substance listed in appendix C of the SUSDP.
- Any substance which is included in a Poisons schedule of the SUSDP without a formal level at which "scheduling" no longer applies (the "cut-off" limit).
- Where a proposed substance is not in itself scheduled or cited in the SUSDP but contains, a significant level of component(s) which are scheduled or cited without limit in the SUSDP, then a proposed substance may be considered ineligible.

Substances scheduled in the SUSDP, for which a cut-off limit applies, may be considered for use in listed medicines with the provision that, if the application is successful, the level of substances in any listed medicines will not exceed the SUSDP Scheduling threshold.

Substance Eligibility - Flowchart of Decisions and Actions **Step 1**



Substance eligible for use in listed medicines
Proceed to application data screen assessment Apply Step 2

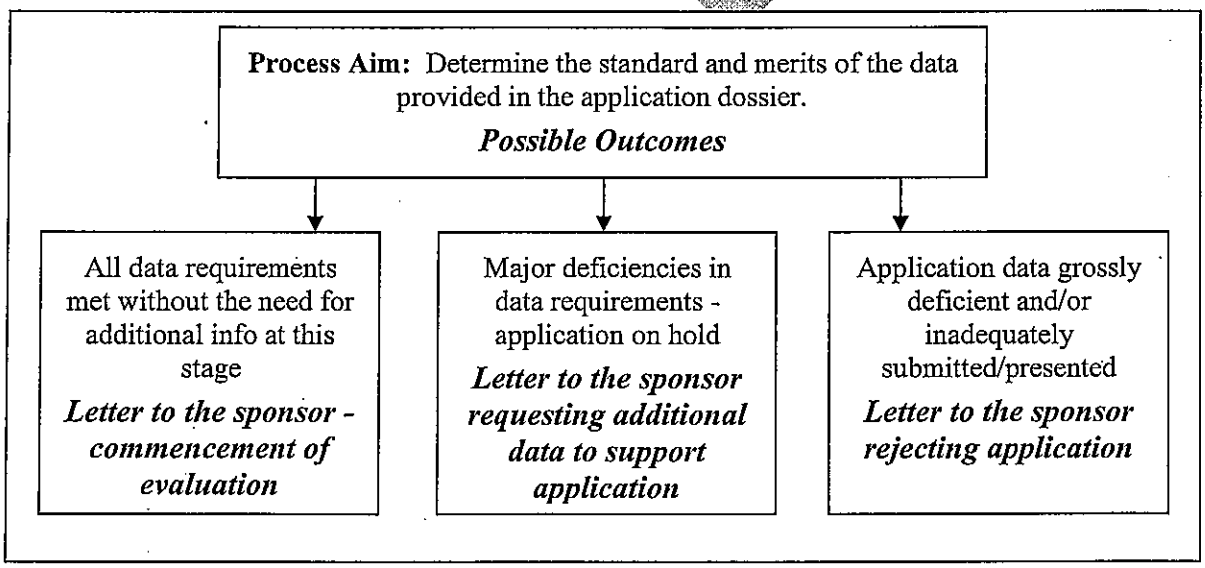
Schedule 4 of the Regulations

Part 1 of Schedule 4 of the Regulations details sources of biological material that are prohibited from use as an ingredient of listed medicines, on the basis of inherent safety concerns, and therefore, are ineligible for evaluation.

Part 4 of Schedule 4 of the Regulations details herbal materials, including specific plant parts, which are prohibited from use as an ingredient in listed medicines, and therefore, are ineligible for evaluation.

When a proposed substance is blocked from use in listed complementary medicines by a regulatory instrument such as the Regulations or the SUSDP, then the application is ineffective and cannot be considered further, regardless of its merits. In such circumstances, the application is rejected.

Flowchart of Decisions and Actions - technical data screening - Step 2



Data requirements

General requirements for new substance application are stipulated in the Part III of the Australian Regulatory Guidelines for Complementary Medicines (ARGCM). Appendix 3 of Part III of the ARGCM provides data requirements for this type of application. This type of application must contain CMQC data for the substance. In addition, the safety of a substance should be supported either by the preclinical safety data (and/or clinical safety data) or data demonstrating history of traditional therapeutic use, as stipulated in ARGCM.

A general screen of application will be conducted using following templates:

- New substance application - pre-evaluation screen - CMQC data (see Attachment 1); and

- New substance application - pre-evaluation screen - preclinical & clinical data (see Attachment 2)

Process to follow

Assuming a substance is eligible for use in listed complementary medicines, the following steps should be undertaken:

- Check for the presence of the information required as part of the dossier using the screen template listed above as an attachment.
- Note deficiencies in the data under the relevant heading and provide a comment.
- If there are only one or two minor deficiencies in the data, the officer screening the technical aspects of the application may choose to comment to this effect and recommend the matter be pursued as part of the evaluation process rather than at the screening stage.
- If the deficiencies in the dossier are numerous (i.e., more than one or two) and/or such that an evaluator could not make conclusions about the product based on the information presented, the screening officer should outline the deficiencies found at the end of the screening template (under the heading 'overall remarks') and clearly recommend what data are required before the application can be accepted for evaluation.
- Alternatively, if the data package is grossly deficient and/or badly formatted, the screening officer may recommend rejection of the application.
- The screening report should be returned to the Principal Scientist for the follow-up action, being one of the following:
  - evaluation commencement letter;
  - pro-forma letter requesting additional information (to be provided usually within 28 days); or
  - pro-forma application rejection letter.

One of the above listed letters will be drafted by the Principal Scientist (when necessary compiling information on deficiencies from both screening reports). Templates for the above letters are found in the S:\CO\TGA\CNPD\CMS\standard operating procedures\Library of letters_2007.

The advice of the Director PREMAS should be sought if there is doubt about the appropriate course of action to adopt.

Rejection of an application

OCM may choose to reject an application where:

a) The correct fee(s) have not been paid at the time of lodgement of the application with the TGA/OCM. Prior to any application rejection on this basis, the Coordinator will have ensured that FSG has alerted the sponsor to the fee(s) deficiency.

b) The application presents an unacceptable format, including:
   - improper use, incomplete, incorrect or no application form;
   - contradictory, ambiguous or unclear wording;

- untranslated (non-English) text;
- gross insufficiency of information; and
- unrealistic or unachievable applications aim(s), with respect to safe usage of the substance in listed medicines (including a block by a regulatory instrument).

c) The sponsor fails to reasonably address any or all requests for additional information to support the application during the pre-evaluation assessment or evaluation phases.

The onus rests with the OCM to ensure that any decision to rejects an application is technically and legally defensible. Further, OCM will ensure that the reasons for the rejection are clearly defined to the sponsor, in the rejection (*pro forma*) letter.

5. References

Therapeutic Goods Act 1989

Therapeutic Goods Regulations 1990

Australian Regulatory Guidelines for Complementary Medicines (ARGCM)

Food Standard Code

Standard for the Uniform Scheduling of Drugs and Poisons (SUSDP)

6. Attachments

1. New substance application - pre-evaluation screen - CMQC data (see Attachment 1); and
2. New substance application - pre-evaluation screen - preclinical & clinical data (see Attachment 2)

New substance application
Pre-evaluation Filter Checklist
Chemistry, manufacturing and quality control (CMQC) data
Office of Complementary Medicines

Application and sponsor details
Substance name:
Sponsor:
Agent:
PATS No:
Date submitted:

Information Assessment Scale

Adequate: sufficient quality and quantity of relevant information to proceed to evaluation phase

Inadequate: application considered workable in this area but insufficient quality and quantity in the relevant information to proceed to evaluation without additional information being supplied.

Unworkable: application considered to be profoundly deficient in the relevant area and is considerable to be unworkable. Major changes required to be undertaken before application can be evaluated.

Assessment

Note the presence of relevant data in the dossier and assess if they appear to be adequate .

1. General Information

Description (composition)

Nomenclature (AAN, AHN)

Structure

General properties (botanical, physico-chemical)

2. Manufacture

Manufacturer

Manufacturing process and process controls

Control of materials

Controls of critical steps or intermediates

Manufacturing process development

3. Characterisation

Monographs

Identity, elucidation of structures and other characteristics

Impurities and incidental constituents

4. Control of active substance

Draft Compositional Guideline

Analytical procedures

Validation of analytical procedures

Batch analyses

Justification of compositional guideline

5. Reference standards or materials

6. Container closure system

7. Stability

Overall remarks

Indicate that application is acceptable for evaluation

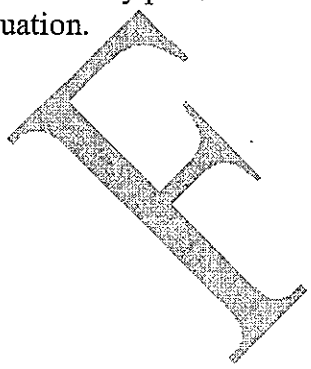
or

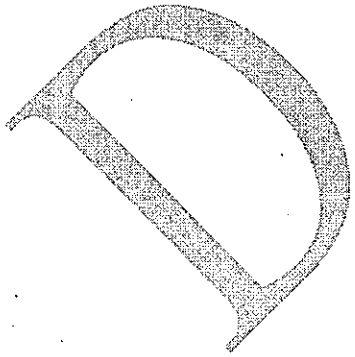
Outline major deficiencies which should be addressed by provision of additional information before the application can be accepted for evaluation.

[Evaluator]

OCM

[date]





New substance application
Pre-evaluation Filter Checklist
Preclinical and Clinical data
Office of Complementary Medicines

Application and sponsor details
Substance name:
Sponsor:
Agent:
PATS No:
Date submitted:

Information Assessment Scale

Adequate: sufficient quality and quantity of relevant information to proceed to evaluation phase

Inadequate: application considered workable in this area but insufficient quality and quantity in the relevant information to proceed to evaluation without additional information being supplied.

Unworkable: application considered to be deficient in the relevant area and is considerable to be unworkable. Major changes required to be undertaken before application can be evaluated.

Preclinical/Tox package – total pages: ???

Clinical data – total pages: ???

Assessment

Note the presence and location of relevant data in the dossier and assess if they appear to be adequate .

3 History and pattern of use

3.1 Traditional Uses

Does application substantially relay on the history of traditional therapeutic use to demonstrate safety of the substance?

3.2 Existing Availability and Regulatory Status

3.2.1 Products available in Australia

3.2.2 Products available internationally

3.3 Posology

4 Biological activity

4.1 Primary pharmacodynamics

4.1.1 In vitro

4.1.2 In vivo

4.2 Secondary pharmacodynamics

4.3 Safety pharmacology

4.4 Pharmacodynamic drug interactions

4.5 Pharmacokinetics

4.6 Pharmacokinetic drug interactions

5 Toxicology

5.1 *In vitro*

5.2 Single-dose toxicity

5.3 Repeat-dose toxicity

5.4 Genotoxicity

5.5 Carcinogenicity

5.6 Reproductive and developmental toxicity

5.7 Local Tolerance

5.8 Other data (specify)

6 Clinical data

7 Adverse reactions

7.1 Australian Adverse Reaction Database Reports

7.2 International Adverse Reaction Databases Reports

7.3 Literature Published Reports

8 References

Are all quoted references provided???

Is the literature search strategy included with search criteria and justification for selection of relevant references provided?

Overall remarks

Indicate that application is acceptable for evaluation

or

Outline major deficiencies which should be addressed by provision of additional information before the application can be accepted for evaluation.

[Evaluator]

OCM

[date]