MEDICINES CONTROL COUNCIL

COMPLEMENTARY MEDICINES - USE OF THE ZA-CTD FORMAT IN THE PREPARATION OF A REGISTRATION APPLICATION

This guideline is intended to provide recommendations to applicants wishing to submit applications for the registration of Complementary Medicines. It intends to invite comment from all stakeholders with the view to present to the Medicines Control Council for authorization. In addition to this guideline, Council reserves the right to request any additional information to establish the safety, quality and efficacy of a medicine in keeping with the knowledge current at the time of evaluation. The MCC is committed to ensure that all registered medicines will be of the required quality, safety and efficacy.

Guidelines and application forms are available from the office of the Registrar of Medicines and the website.

First publication for comment	November 2013
Due date for comment	22 November 2013
Publication for implementation	December 2013
Version 2	March 2014
Version 3	June 2016

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1 INTRODUCTION

This document aims to provide guidance on how to present the applications for registration of a complementary medicine in the Common Technical Document (CTD) format. A guide providing further clarification on the exact location of relevant parts of the documentation and the corresponding guidelines in the CTD Module 3 is included as Appendix 1.

It should be read together with the current versions of the following guidelines, including those referred to therein:

- 7.01 Complementary Medicines – Discipline Specific: Safety and Efficacy
- 7.04 Complementary Medicines – Health Supplements: Safety and Efficacy
- 7.05 Complementary Medicines – Quality
- 2.24 Guidance for the submission of the South African CTD/eCTD – General & Module 1
- 2.01 General Information
- 2.03 Alcohol content of medicines
- 2.04 Post-Importation testing
- 2.05 Stability
- 2.06 Biostudies
- 2.07 Dissolution
- 2.08 Amendments
- 2.14 Patient Information Leaflets (PILs)
- 2.15 Proprietary Names for Medicines
- 2.16 Package Inserts for Human Medicines
- 2.25 Pharmaceutical and Analytical – CTD/eCTD
- 4.01 Guide to Good Manufacturing Practice for Medicines in South Africa
- 16.01 Guideline for Licence to Manufacture, Import or Export

and the forms:

- Application for Registration of a Medicine – South African Common Technical Document (ZACTD)
- 6.15 Screening Template for new application for registration
- 6.10 Licence Application to Manufacture, Import or Export Medicine

2 SCOPE

This guideline applies to the application for registration of complementary medicines submitted inZA-CTD format.

3 ZA-CTD STRUCTURE & GUIDANCE

The table below describes the ZA CTD structure and provides additional guidance to that included in the current guidelines for submission of application in ZA CTD format.

For this guideline the term “Applicable” means that the guidance provided in the “Guidance for the Submission of the South African CTD/eCTD General & Module 1”, “Guideline: Complementary Medicines

– Discipline Specific: Safety and Efficacy" or "Guideline: Complementary Medicines – Health Supplements: Safety and Efficacy" should apply.

If no specific heading exists, the information should be provided under the relevant module as described below.

3.1 ZA Module 1: Administrative information

1.0	**Letter of application**	Applicable
1.1	**Comprehensive table of contents**	Applicable
1.2	**Application**	
1.2.1	**Application form**	Applicable
1.2.2	**Annexes**	
1.2.2.1	Proof of payment	Applicable
1.2.2.2	Letter of authorisation for communication on behalf of the applicant/PHCR	Applicable
1.2.2.3	Dossier product batch information	Applicable
1.2.2.4	Electronic copy declaration	Reserved for eCTD
1.2.2.5	Curriculum vitae of the person responsible for pharmacovigilance	Applicable
1.2.2.6	API change control	Not Applicable
1.2.2.7	EMA certificate for a Vaccine Antigen Master File (VAMF)	Not Applicable
1.2.2.8	EMA certificate for a Plasma Master File (PMF)	Not Applicable
1.3	**South African labelling and packaging**	
1.3.1	South African Package Insert	Applicable
1.3.1.1	Package insert	Applicable
1.3.1.2	Standard References	Applicable
1.3.2	Patient Information Leaflet	Applicable
1.3.3	Labels	Applicable
1.3.4	Braille	Reserved for later use
1.4	**Information about the experts**	
1.4.1	Quality	Applicable (person responsible for information included in Module 2.3)
1.4.2	Non-clinical	Applicable (person responsible for information included in Module 2.4)
1.4.3	Clinical	Applicable (person responsible for information included in Module 2.5)
1.5	**Specific requirements for different types of applications**	
1.5.1	Literature based submissions	Applicable See Guideline for CM – DS/HS: Safety and Efficacy

1.5.2	Amendments/Variations [1]	Applicable
1.5.2.1	Tabulated schedule of amendments	Applicable
1.5.2.2	Medicines Register Details	Applicable
1.5.2.3	Affidavit by Responsible Pharmacist	Applicable
1.5.3	Proprietary name applications and changes	Applicable
1.5.4	Genetically modified organisms	Applicable when relevant
1.5.5	Package Insert / updates	Applicable
1.6	**Environmental risk assessment**	
1.6.1	Non-GMO (genetically modified organisms)	Not required
1.6.2	GMO	Not required. However, there may be exceptional cases where further justification to the absence of an environmental risk assessment may be necessary
1.7	**Good manufacturing practice**	
1.7.1	Date of last inspection of each site	Applicable
1.7.2	Inspection reports or equivalent document	Applicable
1.7.3	Latest GMP certificate or a copy of the appropriate licence	Applicable
1.7.4	Release	Applicable
1.7.4.1	API	Applicable
1.7.4.2	IPIs	Applicable
1.7.4.3	Finished Product Release Control (FPRC) tests	Applicable
1.7.4.4	Finished Product Release Responsibility (FPRR) criteria	Applicable
1.7.5	Confirmation of contract	Applicable
1.7.6	CPP (WHO Certification scheme)	Applicable
1.7.7	SAPC registration	Applicable
1.7.8	Registration with Registrar of Companies	Applicable
1.7.9	Other documents relating to the Applicant/PHCR	Applicable
1.7.10	Sample and Documents	Applicable
1.7.10.1	Confirmation of submission of sample	
1.7.10.2	Batch manufacturing record of the sample	
1.7.10.3	CoA of the sample	
1.7.11	Certified copy of a permit to manufacture specified Schedule 5, Schedules 6, 7 and 8 substances.	Applicable
1.7.12	Inspection flow diagram	Applicable
1.7.13	Organogram	Applicable

[1] Amendments guideline

1.8	**Details of compliance with screening outcomes**	Applicable
1.9	**Individual patient data - statement of availability**	Applicable when relevant
1.10	**Foreign regulatory status**	
1.10.1	List of countries in which an application for the same product as being applied for has been submitted	Applicable Any particular circumstances should be specifically stated.
1.10.2	Registration certificate or marketing authorisation	Applicable English copies / translations are to be provided.
1.10.3	Foreign prescribing and patient information	Applicable
1.10.4	Data set similarities	Applicable
1.11	**Bioequivalence trial information**	Applicable when relevant
1.12	**Paediatric development programme**	Not applicable
1.13	**Risk management plan**	Reserved for future use

3.2 Module 2: Common Technical Document summaries

2.1	**CTD Table of Contents (modules 2 to 5)**	Applicable
2.2	**Introduction**	Applicable
2.3	**Quality Overall Summary (QOS)**	A description of the desired product and product-related substances and a summary of general properties, characteristics, features and characterization data, as described in S.3.1, should be included. The QOS should summarise the data on potential contamination by micro-organisms, products of micro-organisms, pesticides, toxic metals, fumigants, etc. In some specific circumstances, the risk of radioactive contamination is to be considered
2.3.S	Quality Overall Summary - Active Pharmaceutical Ingredient (name, manufacturer)	
2.3.P	Quality Overall Summary - Finished Pharmaceutical Product (name, dosage form)	
2.3.A	Quality Overall Summary - Appendices	
2.4	**Non-clinical Overview**	Applicable when relevant
2.5	**Clinical Overview**	Applicable when relevant
2.6	**Non-clinical Written and Tabulated Summaries**	
2.6.1	Introduction	Tabulated non-clinical summaries are generally not required for well-known substances when a monograph or a pharmacopoeia entry has been established.
2.6.2	Pharmacology Written Summary [2]	
2.6.3	Pharmacology Tabulated Summary (See Appendix B)	

[2] *The CTD defines further heading levels and navigation should be provided within the document to the subheadings.*

2.6.4	Pharmacokinetics Written Summary [2]	When the applicant is requested to supplement the data supporting the monograph with additional safety data (e.g. tests on genotoxicity, reproductive toxicity and carcinogenicity) these data shall be presented in the tabulated non-clinical summaries in this section. When there is no monograph or pharmacopoeia entry, tabulated non-clinical summaries in Module 2 shall be provided.
2.6.5	Pharmacokinetics Tabulated Summary (See Appendix B)	
2.6.6	Toxicology Written Summary [2]	
2.6.7	Toxicology Tabulated Summary (See Appendix B)	
2.7	**Clinical Summary**	Tabulated clinical summaries are generally not required for well-known substances when a monograph or a pharmacopoeia entry has been established. When supplementing data concerning the plausibility of pharmacological effects or efficacy of the product as well as information on the safety of use are addressed in section 2.5, a tabulated summary shall be presented in this section 2.7.
2.7.1	Summary of Biopharmaceutic Studies and Associated Analytical Methods [2]	
2.7.2	Summary of Clinical Pharmacology Studies [2]	
2.7.3	Summary of Clinical Efficacy – *Indication* [2]	
2.7.4	Summary of Clinical Safety [2]	
2.7.5	Literature References	
2.7.6	Synopses of Individual Studies	

3.3 Module 3: Quality

Refer to the Guideline "Complementary Medicines – Quality

3.1	**Table of contents of module 3**	Applicable
3.2	**Body of data**	Applicable
3.2.S	**Active Pharmaceutical Ingredient (name, manufacturer)**	
3.2.S.1	General information *(name, manufacturer)*	Applicable
3.2.S.1.1	Nomenclature *(name, manufacturer)*	Information on the naming of the substances should be provided.
3.2.S.1.2	Structure *(name, manufacturer)*	Applicable
3.2.S.1.3	General Properties *(name, manufacturer)*	Applicable
3.2.S.2	Manufacture *(name, manufacturer)*	Applicable
3.2.S.2.1	Manufacturer(s) *(name, manufacturer)*	Applicable
3.2.S.2.2	Description of Manufacturing Process and Process Controls *(name, manufacturer)*	Applicable
3.2.S.2.3	Control of Materials *(name, manufacturer)*	Applicable
3.2.S.2.4	Controls of Critical Steps and Intermediates *(name, manufacturer)*	Applicable
3.2.S.2.5	Process Validation and/or Evaluation *(name, manufacturer)*	Applicable
3.2.S.2.6	Manufacturing Process Development *(name, manufacturer)*	Applicable
3.2.S.3	Characterisation *(name, manufacturer)*	Applicable

3.2.S.3.1	Elucidation of Structure and other Characteristics *(name, manufacturer)*	Applicable
3.2.S.3.2	Impurities *(name, manufacturer)*	Applicable
3.2.S.4	Control of active pharmaceutical ingredient *(name, manufacturer)*	Applicable
3.2.S.4.1	Specifications *(name, manufacturer)*	Applicable
3.2.S.4.2	Analytical Procedures *(name, manufacturer)*	Applicable
3.2.S.4.3	Validation of Analytical Procedures *(name, manufacturer)*	Applicable
3.2.S.4.4	Batch Analyses *(name, manufacturer)*	Applicable
3.2.S.4.5	Justification of Specification *(name, manufacturer)*	Applicable
3.2.S.5	Reference Standards or Materials *(name, manufacturer)*	Applicable
3.2.S.6	Container Closure System *(name, manufacturer)*	Applicable
3.2.S.7	Stability *(name, manufacturer)*	Applicable
3.2.S.7.1	Stability summary and conclusions *(name, manufacturer)*	Applicable
3.2.S.7.2	Post approval stability protocol and stability commitment *(name, manufacturer)*	Applicable
3.2.S.7.3	Stability Data *(name, manufacturer)*	Applicable
3.2.P	**Pharmaceutical Product *(name, dosage form)***	
3.2.P.1	Description and Composition of the pharmaceutical product *(name, dosage form)*	Applicable
3.2.P.2	Pharmaceutical Development *(name, dosage form)*	Applicable
3.2.P.2.1	Components of the Pharmaceutical Product *(name, dosage form)*	Applicable
3.2.P.2.1.1	Active Pharmaceutical Ingredient(s) *(name, dosage form)*	Applicable
3.2.P.2.1.2	Excipients *(name, dosage form)*	Applicable
3.2.P.2.2	Final pharmaceutical product *(name, dosage form)*	Applicable
3.2.P.2.2.1	Formulation development *(name, dosage form)*	Applicable
3.2.P.2.2.2	Overages *(name, dosage form)*	Applicable
3.2.P.2.2.3	Physicochemical and biological properties *(name, dosage form)*	Applicable
3.2.P.2.3	Manufacturing process development *(name, dosage form)*	Applicable
3.2.P.2.4	Container closure system *(name, dosage form)*	Applicable
3.2.P.2.5	Microbiological attributes *(name, dosage form)*	Applicable
3.2.P.2.6	Compatibility *(name, dosage form*)	Applicable
3.2.P.3	Manufacture *(name, dosage form)*	Applicable
3.2.P.3.1	Manufacturer(s) *(name, dosage form)*	Applicable
3.2.P.3.2	Batch formula *(name, dosage form)*	Applicable
3.2.P.3.3	Description of manufacturing process and process controls *(name, dosage form)*	Applicable

3.2.P.3.4	Controls of critical steps and intermediates *(name, dosage form)*	Applicable
3.2.P.3.5	Process validation and/or evaluation *(name, dosage form)*	Applicable
3.2.P.4	Control of Inactive Pharmaceutical Ingredients *(name, dosage form)*	Applicable
3.2.P.4.1	Specifications *(name, dosage form)*	Applicable
3.2.P.4.2	Analytical procedures *(name, dosage form)*	Applicable
3.2.P.4.3	Validation of analytical procedures *(name, dosage form)*	Applicable
3.2.P.4.4	Justification of specifications *(name, dosage form)*	Applicable
3.2.P.4.5	Excipients of human or animal origin *(name, dosage form)*	Applicable
3.2.P.4.6	Novel excipients *(name, dosage form)*	Applicable
3.2.P.5	Control of pharmaceutical product *(name, dosage form)*	Applicable
3.2.P.5.1	Specification(s) *(name, dosage form)*	Applicable
3.2.P.5.2	Analytical procedures *(name, dosage form)*	Applicable
3.2.P.5.3	Validation of analytical procedures *(name, dosage form)*	Applicable
3.2.P.5.4	Batch analyses *(name, dosage form)*	Applicable
3.2.P.5.5	Characterisation of impurities *(name, dosage form)*	Applicable
3.2.P.5.6	Justification of specifications *(name, dosage form)*	Applicable
3.2.P.6	Reference standards or materials *(name, dosage form)*	Applicable
3.2.P.7	Container closure system *(name, dosage form)*	Applicable
3.2.P.8	Stability *(name, dosage form)*	Applicable
3.2.P.8.1	Stability summary and conclusion *(name, dosage form)*	Applicable
3.2.P.8.2	Post-approval stability protocol and stability commitment *(name, dosage form)*	Applicable
3.2.P.8.3	Stability data *(name, dosage form)*	Applicable
3.2.A	Appendices	Not Applicable
3.2.A.1	Facilities and equipment *(name, manufacturer)*	Not Applicable
3.2.A.2	Adventitious agents safety evaluation *(name, dosage form, manufacturer)*	Not Applicable
3.2.A.3	Excipients	Not Applicable
3.2.R	**Regional Information**	
3.2.R.1	Pharmaceutical and Biological availability	Applicable if relevant
3.2.R.2	Parent API manufacturer with various sites	Applicable
3.2.R.3	Certificate(s) of suitability with respect to the Ph.Eur. (CEPs)	Applicable if relevant
3.2.R.4	Multiple API manufacturers	Applicable
3.2.R.4.1	Comparative API manufacturers study report	Applicable
3.2.R.4.2.	Comparative results	Applicable
3.2.R.4.3	Confirmation of compliance with guidelines	Applicable

3.2.R.4.4	Certificates of analysis	Applicable
3.2.R.5	Medical device	Not Applicable
3.2.R.6	Materials of animal and/or human origin	Applicable
3.2.R.7	Batch records of samples	Applicable
3.2.R.8	Other	Reserved for future use
3.3	Literature references	Applicable

3.4 Module 4: Non-clinical study reports

4.1	**Table of contents of Module 4**	Applicable
4.2	**Study reports**	If applicable. If data are available or have been requested these should be provided and summarised in Module 2.6, for which the corresponding non-clinical overview would be included in Module 2.4
4.3	**Literature references**	Such references should be indexed following the agreed format for the organisation of Module 4.

3.5 Module 5: Clinical study reports

5.1	**Table of contents of Module 5**	Applicable
5.2	**Tabular listing of all clinical studies**	If applicable
5.3	**Clinical study reports**	If applicable. If data are available or have been requested these should be provided and summarised in Module 2.7 for which the corresponding clinical overview would be included in Module 2.5
5.4	**Literature references**	Such references should be indexed following the agreed format for the organisation of Module 5.

4 REFERENCES

1) Guideline on the use of the CTD format in the preparation of a registration application for traditional herbal medicinal products 12 March 2013. EMA/HMPC/71049/2007 Rev. 1
2) Guideline: Complementary Medicines – Discipline Specific: Safety and Efficacy
3) Guideline: Complementary Medicines – Health Supplements: Safety and Efficacy
4) Guideline: Complementary Medicines – Registration Application ZA-CTD - Quality
5) South African Common Technical Document – ZACTD, Application for Registration of a Medicine
6) Guidance for the Submission of the South African CTD/eCTD - General & Module 1
7) Guideline: Pharmaceutical and Analytical - CTD /eCTD
8) Guideline: Stability
9) Guideline: General Information
10) Guide to Good Manufacturing Practice for Medicines in South Africa

5 UPDATE HISTORY

Date	Reason for update	Version & publication
Nov 2013	First publication released for comment	v1 Nov 2013
22 Nov 2013	Deadline for comment	
Dec 2013	Published for implementation	v1 Dec 2013
Mar 2014	Amended to • expand list of guidelines in section 1 • section 3.3: 3.2.S.2.6, 3.2.P.3.5, 3.2.R.3 • sections 3.4 and 3.5 to replace “reports” with “non-clinical overview” and “clinical overview” in 4.3 and 5.3 respectively • include section 4 References • include Appendix 1 with detail on Module 3	v2 Mar 2014
June 2016	Deletion of Appendix A and referral to new guideline on quality of complementary medicines	v3 June 2016