SOUTHERN AFRICAN DEVELOPMENT COMMUNITY

GUIDANCE FOR THE SUBMISSION OF THE SADC MRH/ZAZIBONA CENTRALIZED PROCEDURE MODULE 1 OF THE CTD

Contents

ABBREVIATIONS AND ACRONYMS

API	Active Pharmaceutical Ingredient
CEP	Certificate of Suitability (Ph. Eur. monograph)
CHMP	Committee for Medicinal Products for Human Use (formally, Committee for Proprietary Products) (EU)
CTD	Common Technical Document
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
ICH	International Conference on Harmonisation (of Technical Requirements for Registration of Pharmaceuticals for Human Use)
IPD	Individual Patient Data
IT	Information technology
MS	Member State
NMRA	National Medicines Regulatory Authority
PI	Package Insert
PIL	Patient Information Leaflet
PMF	Plasma Master File
SA	South Africa
SADC	Southern African Development Community
SmPC	Summary of Product Characteristics (European)
US FDA	United States Food and Drug Administration
USA	United States of America
WHO	World Health Organization

INTRODUCTION

Background

This guideline provides recommendations for applicants preparing a Common Technical Document (CTD) for the Registration of Medicines for submission to the Southern African Development Community (SADC) Medicines Regulatory Harmonisation (MRH) centralized procedure which is also known as ZAZIBONA.

In line with Article 29 of the SADC Protocol on Health, harmonization of medicines regulatory systems was identified as a critical component within the context of public health and access to medicines, to achieve the regional common agenda on health. In 2013, SADC Health Ministers and Ministers Responsible for HIV and AIDS approved the adoption of the ICH CTD to facilitate harmonization in the region. This guideline describes a format for the Common Technical Document (CTD) molule 1 that will be acceptable in the SADC centralized procedure. It should be noted that after an application has been recommended for registration in the centralized procedure, the applicant should align module one with country specific requirements when submitting the application to the National Medicines Regulatory Authority (NMRA).

This document provides recommendations on the format and presentation of module 1 for product dossiers (PDs)/applications for registration.

Objectives

These guidelines are intended to provide guidance on the location of regional information (Module 1) and other general data requirements.

These measures are intended to promote effective and efficient processes for the development of PDs and the subsequent assessment procedures.

Granularity of Module 1

Module 1	1.0		
	1.1		
	1.2	1.2.1	
		1.2.2	
		1.2.3	
		1.2.4	
		1.2.5	
		1.2.6	
		1.2.7	
		1.2.8	
	1.3	1.3.1	
		1.3.2	
	1.4	1.4.1	
		1.4.2	
		1.4.3	
	1.5	1.5.1	
		1.5.2	1.5.2.1
			1.5.2.2
			1.5.2.3
			1.5.2.4
	1.6		
	1.7	1.7.1	
		1.7.2	
		1.7.3	
		1.7.4	
	1.8		
	1.9		
	1.10	1.10.1	
		1.10.2	
		1.10.3	
		1.10.4	

		1.10.5	
	1.11	1.11.1	
		1.11.2	
		1.11.3	
		1.11.4	
		1.11.5	
		1.11.6	
	1.12		
	1.13	1.13.1	
		1.13.2	
	1.14		

Documents rolled up to this level are not considered appropriate
One document may be submitted at this level

PART B: MODULE 1

Module 1 should contain all administrative documents (e.g. application forms and certifications), labelling, general correspondence and annexes as needed. Documents should be submitted in English and be organised in the order listed below.

Module 1.0 Cover Letter

Documentation		
1.	1.0	Cover Letter

Applicants should include a *Cover Letter* with all applications. A copy of the letter should be placed at the beginning of Module 1.

Module 1.1 Comprehensive table of contents

Documentation		
1.	1.1	Comprehensive table of contents

Module 1 should include a comprehensive table of contents for the entire application. The comprehensive table of contents should include a complete list of all documents provided in the application by module.

In the table of contents, the location of each document should be identified by referring to the volume numbers that contain the relevant documents and any tab identifiers.

Page numbers only should not be used in the table of contents to refer to documents, rather; tab identifiers as described above should be used. Page numbers in addition to the tab identifier should be used to facilitate location within documents where relevant.

Module 1.2 Application Information

Documentation		
1.	1.2.1	Application Form
2.	1.2.2	Letter of authorisation for communication on behalf of the applicant
3.	1.2.3	API change control
4.	1.2.4	Copy of EMA certificate for a Vaccine Antigen Master File (VAMF)
5.	1.2.5	Copy of EMA certificate for a Plasma Master File (PMF)
6.	1.2.6	Copy of certificate(s) of suitability of the European Pharmacopoeia (CEP)
7.	1.2.7	Copy of confirmation of API prequalification document (CPQ)
8.	1.2.8	Letter of access from the APIMF holder, CEP holder or CPQ holder

1.2.1 Application form

Each application for assessment of a medicine must be submitted in accordance with SADC MRH application form accessible from the ZAZIBONA website.

1.2.2 Letter of authorisation for communication on behalf of the applicant

The suitably qualified person responsible for the compilation of the application must sign the application. This should be an original signature (scanned signature not acceptable). Attach an individualised, person specific letter of authorisation for the signatory, issued by the Person responsible for the overall management and control of the business (CEO).

A letter of Authorisation for the responsible person, if different from the person signing the dossier, to communicate with ZAZIBONA should be submitted in this section.

1.2.3 API change control

A formal agreement exists between the manufacturer of the Finished Pharmaceutical Product (FPP) and each manufacturer of the active pharmaceutical ingredient (API), which ensures that information will be communicated between them and to SADC MRH AND NMRA's before any significant change is made to the site of manufacture, manufacturing procedure or quality control specifications of the API. Except when permitted by the SADC MRH and NMRA's Amendment guidelines relating to changes to medicines, such changes will not be

made to the API(s) to be used in manufacture of medicines to be distributed in SADC before written approval is granted.

A copy of the agreement between API and FPP manufactures should be submitted in this section.

1.2.4 Copy of EMA certificate for a Vaccine Antigen Master File (VAMF)

Insert a copy of the European Medicines Agency certificate for a Vaccine Antigen Master File (VAMF) if applicable.

1.2.5 Copy of EMA certificate for a Plasma Master File (PMF)

Insert a copy of the European Medicines Agency certificate for a Plasma Master File, if applicable.

1.2.6 Copy of certificate(s) of suitability of the European Pharmacopoeia (CEP)

Insert a copy of certificate(s) of suitability of the *European Pharmacopoeia* (CEP) ncluding annexures.

1.2.7 Confirmation of Prequalification (CPQ) of an API

Insert a copy of Confirmation of Prequalification (CPQ) of an API in this section.

1.2.8 Letter of access from the APIMF holder, CEP holder or CPQ holder

Insert a copy of Letter of access from the APIMF holder, CEP holder or CPQ holder in this section

Module 1.3 Labelling and packaging

Documentation	
1.3.1	Package Insert/ SmPC
1.3.2	Patient Information Leaflet

Applicants should include the proposed or approved texts of Package Insert (PI) (Module 1.3.1) and Patient Information (PIL) leaflet (Module 1.3.2) in line with the SADC Guideline on Product Information and Labelling. Please note that country specific sections such as section 8, 9 and 10 of the SMPC do not need to be completed when making an application to the centralised procedure.

Sample labels are not required for this procedure but should be submitted when submitting an application to the NMRA after a positive SADC MRH recommendation.

Module 1.4 Information about the experts

Documentation	
1.4.1	Declaration signed by the expert - Quality
	Information about the Expert - Quality
1.4.2	Declaration signed by the expert - Non-clinical
	Information about the Expert - Non-clinical
1.4.3	Declaration signed by the expert - Clinical
	Information about the Expert - Clinical

Experts must provide detailed reports of the documents and particulars, which constitute Modules 3, 4 and 5.

The requirement for these signed Expert Reports may be met by providing:

- The Quality Overall Summary, Non-clinical Overview / Summary and Clinical Overview / Summary in Module 2,
- A declaration signed by the experts in Module 1.4.
- Brief information on the educational background, training and occupational experience of the experts in Module 1.4.
- In cases concerning well-known active pharmaceutical ingredients, exemption from the submission of sections 1.4.2 and 1.4.3 might be given.

References must be provided for any additional claims not supported by the dossier.

Module 1.5 Specific requirements for different types of applications

Documentation		
1.	1.5.1	Studies and data for generic products
	1.5.2	Same/Separate Applications
	1.5.2.1	Tablets/Capsules/Suppositories/Lozenges
	1.5.2.2	Syrups/Liquids/Solutions (non parenterals) /Creams/ointments
	1.5.2.3	Ampoules, Vials and Large Volume Parenterals
	1.5.2.4	Different applicants/proprietary names for the same formula

1.5.1 Studies and data for generic products

If clinical evidence in support of efficacy is not submitted, studies and data to demonstrate the pharmaceutical and/or biological availability of the product should be included. If in the opinion of the applicant no data are required to substantiate efficacy (e.g. parenteral solutions) the rationale for accepting safety and efficacy, including reference to standard Reference Books, should be clearly stated. Refer to Registration Guideline and SADC Bioavailability / Bioequivalence Guideline. [3]

1.5.2. Same/Separate Applications

1.5.2.1 Tablets/Capsules/Suppositories/Lozenges

(i) Different pack-sizes of the same strength and formulation will require one application

(ii) Different strengths and/or formulations will require separate applications.

1.5.2.2 Syrups/Liquids/Solutions (non parenterals)/Creams/ointments

(i) Different container sizes of the same strength and formulation will require one application.

(ii) Same container size of different strengths and/or formulations will require separate applications.

1.5.2.3 Ampoules, Vials and Large Volume Parenterals

(i) Ampoules containing identical solutions of the same strength but of different volumes will require separate applications;

(ii) Ampoules containing solutions of different strengths will require separate applications;

(iii) Ampoules and/or single dose vials containing dry powder, crystals etc, of different mass will require separate applications;

(iv) Ampoules and single dose vials containing the same respective masses of dry powder, crystals etc, will require separate applications;

(v) Ampoules, single dose vials, as well as disposable syringes and cartridges containing identical solutions of the same strength and same volume of liquid will require separate application

(vi) Dental cartridges containing fluids of different volumes will require one application;

(vii) Ampoules containing "water for injection", but of different volume will require one application.

(viii) Special ampoules of dry powder and "water for injections" contained in the same unit, but intended for mixing at the time of injection, will require one application.

(ix) Ampoules containing identical solutions of different volumes used only as a diluent in the reconstitution of a preparation for parenteral use, will require separate applications;

(x) Multi-dose vials of the same strength and formulation in different volumes will require one application,

(xi) Multi-dose vials and a single dose ampoule of the same formulation will require separate applications.

(xii) Multi-dose vials containing dry powder of different mass and the same formulation, and having the same concentration when reconstituted will require one application;

(xiii) A container of diluent to be used with any preparation in (iii), (iv) or (xii) will require one application provided that the diluent is also fully described in the dossier together with the product;

(xiv) An ampoule of diluent to be used with any biological preparation will require one application;

(xv) Infusion solutions of the same or different volumes and of the same formulation, which are packed in containers of exactly the same type of material, will require separate applications;

(xvi) Infusion solutions of the same or different volumes and of the same formulation, which are packed in containers made of different types of materials, will require separate applications;

(xvii) A preparation, packed in plastic containers and intended also to be marketed in glass containers containing the same volume and the same formulation, it will require one application provided the following data are submitted: -

(a) Characteristics of the rubber stopper;

(b) Specifications for the glass;

(c) A comprehensive manufacturing process with particular reference to the washing and sterilization cycles and apparatus used;

(d) Data on particulate matter (contamination);

(e) Stability data with reference to the effect of the pH of the solution.

(xviii) Products with the same strength and formulation but with different colours and/or flavours will require separate applications;

(xix) Applications containing the same active ingredient(s), and where additional indications are sought, where such new indications render the product in a different scheduling status, or different pharmacological classification or have any other restrictions imposed other than the original application, will require separate registration.

1.5.2.4 Different applicants/proprietary names for the same formula

(a) Same formula applied under different proprietary names will require separate applications.

(b) Same formula from different applicants will require separate applications

Module 1.6 Environmental risk assessment

An application should be accompanied by an environmental risk assessment, evaluating any potential risks of the medicinal product to the environment.

The requirements relate to those risks to the environment arising from use, storage and disposal of medicinal products and not for risks arising from the synthesis or manufacture of medicinal products.

In case of extensive documentation for the environmental risk assessment should always be provided in a separate volume as part of Module 1. In case of a short statement, this can remain in the Module 1 volume(s).

Module 1.7 Good manufacturing practice

Documents required by the Inspectorate		
1.	1.7.1	Date of last inspection of each site
2.	1.7.2	Inspection reports or equivalent document
3.	1.7.3	Latest GMP certificate API and FPP or a copy of the appropriate licence
4.	1.7.4	Certified copy of permit to manufacture specified controlled substances

For all medicines, irrespective of the country of origin, it is expected that key manufacturing and/or processing steps in the production of active ingredients and finished pharmaceutical products are performed in plants of acceptable standards (see WHO GMP Guideline).[1]

1.7.1 Date of last inspection of each site

The applicant should provide a list of manufacturers', packers' and Finished Product Release Controls' (FPRCs') names and licence numbers, with a list of the dates of inspection by the Health Authorities of ICH founding and standing members, PIC/S and SADC.

1.7.2 Inspection reports or equivalent document

The applicant should provide copies of inspection reports or equivalent document, not older than three years, from the site conducted by ICH founding and standing members, PIC/S and SADC.

1.7.3 Latest GMP certificate or a copy of the appropriate licence

Include the latest GMP certificate, not older than three years, for manufacturer/s, packer/sand FPRCs or a copy of the appropriate licence.

1.7.4 Certified copy of a permit to manufacture specified controlled substances

Include a duly certified permit to manufacture controlled substances where applicable.

Module 1.8 Details of screening

Documentation:	
1.	Screening Checklist

[1] www.who.int

A copy of the completed screening checklist must be included in module 1.8

Module 1.9 Individual patient data - statement of availability

Documentation:	
1.	Declaration concerning availability of individual patient data

Include a statement that raw clinical and pre-clinical data have been removed from the application and that individual patient data are available on request.

Data in respect of each individual patient from each clinical trial are not required to be included in the documentation at the time of application, except in the case of any bioavailability studies where individual patient data (IPD) for plasma concentrations and derived data are required.

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Module 1.10 Foreign regulatory status

Documentation:		
1.	1.10.1	List of countries in which an application for the same product as being applied for has been submitted, approved, rejected or withdrawn
	1.10.2	WHO type CoPP
	1.10.3	Registration certificates or marketing authorisation
	1.10.4	Foreign prescribing and patient information
	1.10.5	Data set similarities

Applicants are advised that this module should be completed for all applications (including those for multisource products).

1.10.1 List of countries in which an application for the same product as being applied for has been submitted, approved rejected or withdrawn

The applicant should provide, in Module 1.10.1 of the dossier, a list of countries in which an application for the same product as being applied for has been submitted, approved, rejected or withdrawn, including dates of submission (if available).

Reasons for rejection or withdraw should be provided

If no application has been submitted for registration in the country of origin, include a statement to provide the reason for this decision.

1.10.2 WHO type CoPP

A copy of the WHO- type Certificate of a Pharmaceutical product should be submitted in this section.

1.10.3 Registration certificates or marketing authorisation

In the case of registration in the country of origin, or where a marketing authorisation has been granted by a NMRA of ICH founding and standing members, SADC MS and other countries that maybe recognised by SADC MRH, copies of the registration certificates or marketing authorisation should be supplied in this section.

1.10.4 Foreign prescribing and patient information

In the case of marketing authorisations in country of origin, or where marketing authorisation has been granted by the NMRA of ICH founding and standing members, SADC MS and others countries that maybe recognised by SADC MRH, copies of relevant PI/SmPC and PIL should be submitted in this section.

1.10.5 Data set similarities

Module 1.10.4 should contain a summary of the similarities / differences in the product submitted in other countries ICH, SADC and others countries that maybe recognised by individual SADC MS

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Module 1.11 Regional Summaries

Documentation		
1.	1.11.1.1	Study Title(s) (or brief description giving design, duration, dose and subject population of each study)
	1.11.1.2	Protocol and study numbers
	1.11.1.3	Investigational products (test and reference) details in tabulated format, including
		□ active ingredient
		□ strength
		□ dosage form
		□ manufacturer

		□ batch no
		□ expiry or retest date
		□ country in which procured
	1.11.1.4	Confirmation that the test product formulation and manufacturing process is that being applied for
	1.11.1.5	Name and address of the Research Organisation(s) / Contract Research Organisation(s) where the bioequivalence studies were conducted
	1.11.1.6	Sponsor and responsible sponsor representative: name and address, contact details
	1.11.1.7	Duration of Clinical phase: dates of dosing and last clinical procedure
	1.11.1.8	Date of final report
	1.11.2	Biostudy reference product confirmation
	1.11.3	Certificates of analysis of the test and reference products
	1.11.4	Bioequivalence trial information form (BTIF)
	1.11.5	Biowaiver requests in relation to conducting comparative bioavailability study
	1.11.6	Quality Information Summary (QIS)
	1.11.7	Quality Overall Summary (QOS)

Proof of procurement of the biostudy reference product (may include cross-reference to Module 5.3.1)

1.11.2 Biostudy reference product Confirmation

Confirmation that the appropriate reference product was used in the comparative bioavailability study may be provided in the form of a purchase receipt(s) from the supplier, signed confirmation in writing that the reference was purchased in an acceptable market such as ICH founding and standing members, and a photocopy of the product label(s) which clearly shows the trade name, product strength, lot #, and expiry date, of the product administered in the biostudy. In addition, proof of the storage conditions from the time of purchase to study initiation should be provided in this section.

1.11.3 Certificates of analysis of the test and reference products

Certificates of Analyses should be provided in this section in order to verify the potency (as a percent of the label claim) for both the Test and Reference products.

1.11.4 Bioequivalence trial information form (BTIF)

A completed BTIF should be submitted in word format.

1.11.5 Biowaiver requests in relation to conducting comparative bioavailability study

Generally, results from comparative bioavailability studies should be provided in support of the safety and efficacy of each proposed product and of each proposed strength. In the absence of such studies, a justification supporting a waiver of this requirement should be provided in this section for each product and each strength.

A completed Biowaiver Application Form should be submitted in word format. The request for waiver should include supporting data (e.g., comparative dissolution data) which should be provided in the relevant module(s) of the CTD submission (i.e., Modules 2-5). For example, comparative dissolution profiles should be provided in Module 3, section 3.2.P.2 (Pharmaceutical Development).

Requirements for biopharmaceutic studies are described in the SADC Bioavailability/Bioequivalence Guideline and ICHM9 Guideline on Biopharmaceutics Classification System-Based Biowaivers.

1.11.6 Quality Information Summary QIS

Insert a copy of Quality Information Summary QIS. The QIS should be submitted with all additional information and amendment or variations. The QIS template should be completed to provide a condensed summary of the key quality information for the application and constitutes part of the submission package. The QIS provides an accurate record of technical data in the dossier at the time of registration. The QIS is a condensed version of the QOS and represents the final agreed upon key API and FPP information from the dossier assessment (inter alia identification of the manufacturer(s)/site addresses, API/FPP specifications, stability conclusions and relevant commitments).

The QIS template is structured according to the numbering and section headings of the ICH M4Q (CTD-Q) guideline to permit the rapid assembly of the QIS by copying requisite information from the corresponding portions of the QOS filed with the dossier. It is acknowledged that the numbering of the sections in the QIS may not be entirely sequential. Those sections not considered necessary to be included in the QIS have been removed (e.g. 2.3.S.5 Reference standards or materials) and the remaining sections have retained their numbering to be consistent with the original product dossier.

The QIS will serve as an official reference document in the course of GMP inspections, variation assessments and product renewals.

1.11.7 Quality Overall Summary (QOS)

A completed QOS should be submitted in word format.

Module 1.12 Paediatric development program

Documentation		
1.	1.12	References to paediatric development program

There is a recognised global problem with the availability of paediatric specific formulations and a lack of information from proper investigations of the use of medicines in children. This problem leads to medicines being used outside of their approved indications, and, at times, being reformulated by pharmacists to make them more suitable for use by children. However, the basic precept that children should not be discriminated against by being supplied poorly investigated medicines has been accepted internationally.

The CTD guidelines require that the safety and efficacy in the paediatric population should be routinely analysed in applications for a proposed indication that occurs in children.

Please state whether there is a paediatric development program for this medicine and if so, the relevant sections of the dossier.

Module 1.13 Information relating to pharmacovigilance

1.13.1 Pharmacovigilance system

A plan on pharmacovigilance should be submitted in this section

1.13.2 Risk management System

A plan on risk management and or minimisation should be submitted in this section

Module 1.14 Samples

Pictures of the actual medicinal product (for example tablets) should be provided. Product samples will only be submitted upon request.

References

1. Guidelines on submission of documentation for a multisource (generic) finished product. General format: preparation of product dossiers in common technical document format In: *WHO Expert Committee on Specifications for Pharmaceutical preparations. Forty-fifth report.* Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 15
2. SADC Bioavailability/Bioequivalence Guideline.
3. CHMP *Note for Guidance of Bioavailability and Bioequivalence* (CPMP/EWP/QWP/1401/98).
4. Draft Guidance for Industry. Preparation of Comparative Bioavailability Information for Drug
5. Submissions in the CTD format, Health Products and Food Branch, Ministry of Health, Canada.
6. ICH M9 Guideline on Biopharmaceutics Classification System-Based Biowaivers
7. SADC Guideline on Product Information and Labelling