SADC MRH PROJECT

GUIDANCE FOR THE PREPARATION AND SUBMISSION OF DOSSIERS IN COMMON TECHNICAL DOCUMENT FORMAT

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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
GMO	Genetically Modified Organism
GMP	Good Manufacturing Practice
ICH	International Conference on Harmonisation (of Technical Requirements for Registration of Pharmaceuticals for Human Use)
IPD	Individual Patient Data
IPI	Inactive Pharmaceutical Ingredient
IT	Information technology
MHRA UK	Medicines and Health products Regulatory Authority
MS	Member State
NMRA	National Medicines Regulatory Authority
Pdf	Portable document format
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)
TGA	Australian Therapeutic Goods Authority
UK	United Kingdom
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) Member States.

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.

While the SADC Regional Guidelines for Registration of Medicines provides a minimum standard on technical requirements within the region, there has been no harmonisation of the organization of the registration documents. Each SADC Member State (MS) has its own requirements for the organization of the technical reports in the submission of applications for registration of human medicines. To avoid the need to generate and compile different registration dossiers, this guideline describes a format for the Common Technical Document (CTD) that will be acceptable in all SADC MS.

The document describes how to organise applications based on the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines on the CTD.

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

Objectives

These guidelines are intended to:

- Standardise registration requirements for the SADC region thereby facilitating harmonization.
- Fully adopt the modular format of the CTD as developed by ICH;
- Assist applicants in the preparation of PDs/applications by providing clear general guidance on the format of these dossiers; and
- 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 these PDs and the subsequent assessment procedures.

Rationale For Adopting ICH CTD Format

To ensure that the SADC regional standards are aligned with global standards, these are based on the International Conference on Harmonisation of Technical Requirements for Registration of Human Medicines (ICH) guidelines on CTD format, and the World Health Organization (WHO) Guidelines for Registration of multisource (generic) medicines. Adopting the ICH CTD format will assist

applicants to prepare registration dossiers in a single format that can be submitted to all the SADC MS, promote information exchange among the regulators, more efficient assessment, align the region with global standards such as ICH and WHO and ultimately increase availability of medicines to the public. The intended benefits of adopting the ICH CTD format are in-line with the SADC agenda on regional integration and cooperation

Scope

The guidelines will apply in all SADC member states namely Angola, Botswana, Democratic Republic of Congo, Lesotho, Madagascar, Malawi, Mauritius, Mozambique, Namibia, Swaziland, South Africa, Tanzania,
Zambia and Zimbabwe. These guidelines apply to both generic (multisource) and new medicines (innovator).

ORGANISATION OF PRODUCT DOSSIER IN COMMON TECHNICAL DOCUMENT FORMAT

According to the CTD format, each application is a collection of documents, grouped into 5 modules.

This guideline provides information on the contents of the *SADC CTD Module 1: Administrative Information,* as Module 1 is region specific. In addition, the SADC regional CTD format describes the format and organisation of the Summaries, Quality, Non-clinical, and Clinical modules (Modules 2 to 5, respectively).

The CTD guidelines, together with the *SADC Registration Guidelines* provide detailed information about the contents of an application. These guidelines apply to applications to register medicines and all related variations. Applicants should not modify the overall organisation of the CTD. If not contained in the bulk of the documentation, any additional data should be include das addenda to the relevant part, together with additional expert comment that may be provided as a supplement to, or incorporated into, the relevant summary, overall summary or overview.

Module 1 - Administrative information and prescribing information

Relevant administrative documentation should be submitted in Module 1 of the CTD dossier. This module should be divided into the relevant sections, as described in Part B of this guideline.

Module 2 - Summary of the dossier

Module 2 of the CTD dossier contains the summaries and overviews for the quality, non-clinical and clinical sections of the dossier (refer to the European *Notice to Applicants: Medicinal products for human use. Volume 2B: Presentation and format of the dossier CTD* (July 2003).

The Clinical Overview should include a statement regarding Good Clinical Practice (GCP) compliance.

In cases concerning generic, the NMRA may grant exemption from the submission of Non-clinical and Clinical Overviews and Summaries (2.4, 2.5, 2.6 and 2.7). For generics, the following sections should be submitted:

2.1 Table of contents for Module 2

2.2 Introduction

2.3 Quality overall Summary

Module 3 – Quality

Module 3 of the dossier contains the chemical, pharmaceutical and biological data relevant to the application.

Refer to the Registration guideline for the current requirements for this module.

Full reports on biopharmaceutics studies, including methodology and validation data for bioavailability studies, should be included in Module 5.3.1.

Module 4: Non Clinical Study reports

Module 4 of the dossier contains the non-clinical (pharmaco-toxicological) data relevant to the application.

For detailed information and guidance on information for new medicines, the human study reports and related information should be presented in the order described in ICH M4S. Reference should be made to the most current version of the Guidelines

Generally, module 4 is not applicable for generic medicines.

Module 5: Clinical study reports

Module 5 of the dossier contains the clinical data relevant to the application. In most circumstances, the clinical studies included in Module 5 of the dossier will be international studies used to establish the pharmacodynamics, pharmacokinetics, safety and efficacy of the medicine across an international patient population. However, where there is evidence to suggest that the pharmacokinetics or pharmacodynamics of the product may vary across the populations that will use the medicine in SADC MS; the sponsor should consider submitting studies relevant to those target populations.

For detailed information and guidance on presentation of information for new medicines, the human study reports and related information should be presented in the order described in ICH M4E.

Module 5: Clinical study reports

5.1 Table of contents for Module 5

5.2 Tabular listing of all clinical studies

5.3 Clinical study reports

5.3.1 Reports of biopharmaceutical studies

Partial or total exemption from the requirements of Module 5.3.1 may be applicable if efficacy and safety are to be established by clinical data (or for other reasons as determined by the respective

SADC MS NMRA), provided that clinical trials have been conducted with the same formulation as the one being applied for.

5.3.1.1 Bioavailability (BA) study reports

BA studies in this section should include

- studies comparing the release and systemic availability of a drug substance from a solid oral dosage form to the systemic availability of the drug substance given intravenously or as an oral liquid dosage form
- dosage form proportionality studies, and food-effect studies.

5.3.1.2 Comparative bioavailability and bioequivalence study reports

For further guidance on bioavailability/ bioequivalence or biowaiver applications, the applicant should refer to the SADC guidelines for Bioavailability/Bioequivalence guidelines

5.3.1.3 In vitro–in vivo correlation study reports if available

5.3.1.4 Reports of bioanalytical and analytical method for human studies

For further guidance on bioavailability/ bioequivalence or biowaiver applications, the applicant should refer to the SADC guidelines for Bioavailability/Bioequivalence guidelines, bioanalytical method validation guidelines from the US FDA or European Medicines Agency.

5.3.7 Case-report forms (CRFs) and individual patient listings:

For clinical efficacy and safety studies: Only CRFs for subjects who experienced serious adverse events should be included. All CRFs should be available upon request.

For bioequivalence studies: all CRFs for all subjects should be submitted (refer to Bioavailability / bioequivalence guideline for more information)

5.4 Literature references

References to the scientific literature relating Module 5 should be included in this section of the PD when appropriate.

In cases concerning generic, the SADC MS may grant exemption from the submission of Clinical study reports, other than bioequivalence study reports, in Module 5. To justify exemption from the requirements of Module 5.3.1 it should be clearly stated and confirmed: that clinical trials have been performed with the formulation being applied for in Module 3.2.P.1 and that the requirements in Module 5.3.1.2 have been addressed.

The majority of applications for generic medicines are supported by one or more pivotal comparative bioavailability studies. When filing an application in the CTD format for these generic medicines, it is anticipated that only the following relevant sections of Module 5 will normally be required:

5.1 Table of contents for Module 5

5.2 Tabular listing of all clinical studies

5.3 Clinical study reports

5.3.1 Reports of biopharmaceutical studies

5.3.1.2 Comparative bioavailability and bioequivalence study reports

5.3.1.3 In vitro–in vivo correlation study reports if available

5.3.1.4 Reports of bioanalytical and analytical method for human studies

5.3.7 Case-report forms (CRFs) and individual patient listings

5.4 Literature references

SADC GUIDELINES ON QUALITY, SAFETY AND EFFICACY

The technical content of the documents in the CTD modules is outside the scope of this guidance. The CTD guidelines do not indicate the data or studies required; they merely indicate an appropriate format and organisation for the data that have been acquired. The main Registration Guideline and the relevant guidelines (SADC, WHO, ICH or EU) as indicated should be consulted.

PART A: GENERAL INFORMATION FOR APPLICATIONS

Please read together with the Registration guideline.

1 Preparing and organising the Common Technical Document

To facilitate the review of the basic data and to help an evaluator become oriented with the application contents, the display of information should be unambiguous and transparent throughout the CTD.

If additional or supplementary data are submitted, the module(s) should be identified and numbering should follow from the original documentation.

The applicant should not submit the modules that are not used i.e. it is unnecessary to include "not applicable" pages against unused CTD headings.

For new applications, detailed statements justifying the absence of data or specific CTD sections should be provided in the relevant Quality Overall Summary (QOS) and/or Non-Clinical/Clinical Overviews (Module 2.3, 2.4, 2.5). If relevant, justification for empty sections in Module 1 is to be provided in the cover letter.

Acronyms and abbreviations should be defined the first time they are used in each module.

2 Documentation

2.1 Electronic review documents

Electronic submission of documentation (CD or DVD) should be submitted in Microsoft Word (required for templates/summaries, e.g. QOS, BTIF) and text-selectable PDF format (other documentation).

Guidance on eCTD submissions will be provided in future.

3 Organising documents

Each section of the dossier is to be marked by use of clearly annotated tabs and the documentation should be filed in accessible files. Lever arch files are not acceptable. Documents can be combined in volumes as long as appropriately named tab identifiers separate them. For example, the Package insert should be separated from the other documents by a tab identifier. In general, documents from different CTD modules should not be included in the same volume. Documents from different modules may be combined in the same volume for amendments consisting of a small number of short documents.

Administrative documents (e.g. Application letter, Statement on the availability of Individual Patient Data) are included in Module 1. The organisation of such documents should be consistent with the structure described in this guideline. Since these administrative documents are small, they should be placed in the same volume, separated by tab identifiers.

4 Volume identification

Volumes must be numbered by module, resulting in a separate set of numbers for each module.

The labelling of each volume should include:

- Name of applicant
- Name of medicine
- Module and Volume number. The volumes in each module should be numbered separately and sequentially using the format: *x of y volumes*, where x is the number for the specific volume and y is the total number of volumes submitted for the respective module, e.g. Module 3, Vol.1of 6.
- Copy number: The copies of Modules 1, 2 and 3should be numbered as copies *x of y.*
- Contents. Each volume must also be labelled according to the section(s)which it contains, e.g.:

Section 3.2.P.4 means:

3. –Module 3 - Qualities

2. – Body of data

P.–Product

4. – Control of excipients

5 Pagination

A document is a set of pages, numbered sequentially and divided from other documents by a tab.

Page numbering should be at the document level and not at the volume or module level. (The entire submission should never be numbered consecutively by page.) In general, all documents should have page numbers. Since the page numbering is at the document level, there should only be one set of page numbers for each document.

Cross-referencing to documents should be made by referring to the CTD module, volume, tab identifier, and page number (for example: *"see Module 3, Vol. 6, P.4.3 Method validation, p 23"*).

Documents must be printed on both sides of a page, legibility must not be impaired and margin space must be sufficient on both the left and right side, so that information is not obscured when the page is placed in a binder. However, Module 1.3 Labelling and packaging (1.3.1.1, 1.3.2, 1.3.3) must be copied single-sided. Copying of each document must start on a new page and must be separated from the next document by a tab.

6 Paper size

Standard A4 paper should be used for all submissions. Text and tables should be prepared using margins that allow the document to be printed on A4 paper. The left-hand margin should be sufficiently large that information is not obscured through binding.

7 Fonts

Font sizes for text and tables should be of a style and size that are large enough to be easily legible, even after photocopying or when provided electronically**.** *Arial / Times New Roman 12* point font is preferred for narrative text, but printing in a font size with a legibility equivalent to at least Arial 10 point black on white could be used. The copies, including figures, tables and photos should be clearly legible. Shading and/or coloured filling/background and/or print, e.g. in tables and headers, or across pages, is unacceptable and should be avoided.

8 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	
		1.2.9	
		1.2.10	
	1.3	1.3.1	
		1.3.2	
		1.3.3	
		1.3.4	
	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	1.6.1	
		1.6.2	
	1.7	1.7.1	
		1.7.2	
		1.7.3	
		1.7.4	

		1.7.5	
	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		
	1.15	1.15.1	
		1.15.2	

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 organised in the order listed below.

Generally, all of the documents in Module 1, other than the annexes, can be provided in a single volume. The annexes to the module should be submitted in separate volumes.

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. In general, the name for the tab identifier should be the name of the document (section heading according to the CTD format e.g. 3.2.P.4.2). If the full name of the document is too long for the tab identifiers, an alternative name that adequately identifies the document should be substituted.

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	Proof of payment
3.	1.2.3	Letter of authorisation for communication on behalf of the applicant
4.	1.2.4	Electronic copy declaration
5.	1.2.5	API change control
6.	1.2.6	Copy of EMA certificate for a Vaccine Antigen Master File (VAMF)
7.	1.2.7	Copy of EMA certificate for a Plasma Master File (PMF)
8.	1.2.8	Copy of certificate(s) of suitability of the European Pharmacopoeia (CEP)
9.	1.2.9	Copy of confirmation of API prequalification document (CPQ)
10.	1.2.10	Letter of access from the APIMF holder, CEP holder or CPQ holder

1.2.1 Application form

Each application for registration of a medicine must be submitted in accordance with the requirements of the Member State (number of copies, etc.)

(i) All forms are to be completed in English, or official language of preference by Member State.

(ii) Application forms are available from the regulatory authority of each Member State and all completed applications are to be submitted to the appropriate addresses of the respective Regulatory Authority

(iii) An application not submitted in the appropriate format, incomplete or illegible will be rejected.

The application form must also be submitted together with the *1.11.6 Quality information summary (QIS)* with every response to a SADC MS NMRA recommendation and/or an application for amendment of the dossier.

In addition to the paper dossier, Module 1.2.1 should be submitted electronically on CD or DVD.

An application for registration of a medicine may be made by:

(i) The prospective holder of the marketing authorization/registration, hereinafter referred to as the applicant

(ii) A nominee of the applicant who must submit evidence of empowerment of power of attorney

1.2.2 Proof of payment

The application fees applicable to each country should be paid as required. An application not accompanied by the appropriate fee will not be accepted. A copy of the proof of payment should be included in this section.

1.2.3 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 NMRA of a SADC MS should be submitted in this section.

1.2.4 Electronic copy declaration

Both paper and electronic submissions must comply fully with the Common Technical Document as regards presentation and content of the dossier. Any documents submitted on CD/DVD have to be declared identical to that in the paper submission.

1.2.5 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 the NMRA 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 NMRA's Amendments guideline 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 by the NMRA. Both parties understand that the consequences of failure to obtain approval for changes where approval is necessary may include deregistration and recall of batches of medicines containing this material in SADC Member State

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

1.2.6 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.

1.2.7 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.

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

Insert a copy of certificate(s) of suitability of the *European Pharmacopoeia* (CEP) (Including any annexes)

1.2.9 Confirmation of Prequalification (CPQ) of an API

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

1.2.10 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
1.3.3	Labels
1.3.4	Braille

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). Labels complying with specific Member State requirements should be submitted in Module 1.3.3 (mock-ups, specimens or text).

1.3.1 Package Insert/ SmPC

Modules 1.3.1 should include a copy of the PI - either the proposed PI in the case of a new application, or the currently approved PI in the case of amendments. The PI should comply with local requirement of each SADC Member State.

1.3.2 Patient Information Leaflet

Module 1.3.2 should contain a copy of the proposed patient information leaflet (PIL), which should be written in layman's language.

1.3.3 Labels

Labels should be prepared as per national requirements of each SADC Member State

If the applicant has a specimen or mock-up of the sales presentation of the medicine available at the time of initial application, it should be included in Module1.3.3.

A mock-up is a copy of the flat artwork design in full colour, providing a replica of both the outer and immediate packaging, providing a two-dimensional presentation of the packaging / labelling of the medicine. It is also referred to as a paper copy or computer generated version.

A specimen is a sample of the actual printed outer and inner packaging materials and package leaflet. If there are multiple strengths and/or pack sizes, all representative specimens or mock-up should be submitted. If batch number and expiry date are to be printed on the label during packaging, a statement to this effect should accompany the labels.

1.3.4 Braille

For future use.

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, the Council may grant exemption from the submission of sections 1.4.2 and 1.4.3.

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]

For package insert amendments, refer to the Package Insert Guideline.

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	Registration of Responsible Pharmacist or Suitably Qualified Person for local manufacturers
5.	1.7.5	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, PIC/S, SADC and other countries as specified by MS.

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, PIC/S, SADC and other countries as specified by MS.

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 Registration of Responsible Pharmacist or Suitably Qualified Person for local manufacturers

Proof of current registration of the Responsible Pharmacist or Suitably Qualified Person by the relevant registering Body in the SADC MS should be submitted in this section

1.7.5 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

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

If new document versions are submitted, an updated version of Module 1.2.1 must also be submitted.

[1] www.who.int

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.

. Individual patient data may be requested by the NMRA:

- to support a particular study if, during the evaluation, there is any reason to doubt the analysis or conclusions reached;
- if, after registration, the application is selected for auditing of the summary results and conclusions.

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, SADC and others countries that maybe recognised by individual SADC MS, 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, SADC and others countries that maybe recognised by individual SADC MS, 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		
	1.11.1	Summary of Bioequivalence Studies
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)

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 or ICH associated countries, 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 both in hard copy and electronic (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 both in hard copy and electronic (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. [3]

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.

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 Electronic review documents (e.g. product information, BTIF, SADC-QOS)

Electronic copies of the BTIF, SADC-QOS and Biowaiver application forms should be submitted

Module 1.15 Sample and Documents (e.g. FPP, device(s), certificates of analysis)

1.15.1 Confirmation of submission of a sample

All medicine applications for registration must include such number of samples as required by SADC NMRA.

1.15.2 CoA of the sample

Include the CoA of the FPP. Ensure that the batch number on the CoA corresponds with the batch number on the sample.

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

Submissions in the CTD format, Health Products and Food Branch, Ministry of Health, Canada. 2004

UPDATE HISTORY

Date	Reason for update	Version & publication