SAHPRA
SOUTH AFRICAN
HEALTH PRODUCTS
REGULATORY AUTHORITY

GUIDANCE[1] FOR THE SUBMISSION OF THE SOUTH AFRICAN CTD /eCTD - GENERAL & MODULE 1[2]

This guideline is intended to provide recommendations to applicants wishing to submit applications for the registration of medicines. It represents the South African Health Product Regulatory Authority's (SAHPRA) current thinking on the safety, quality and efficacy of medicines. It is not intended as an exclusive approach. SAHPRA 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. Alternative approaches may be used but these should be scientifically and technically justified. SAHPRA is committed to ensure that all registered medicines will be of the required quality, safety and efficacy. It is important that applicants adhere to the administrative requirements to avoid delays in the processing and evaluation of applications.

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

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[1] Based originally on the "Australian Notice to Applicants"- TGA Edition September 2007

[2] CTD Module 1, current version

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ABBREVIATIONS AND ACRONYMS

Act	The Medicines and Related Substances Act, 1965 (Act 101 of 1965) as amended
API	Active Pharmaceutical Ingredient
CC	Clinical Committee
CEP	Certificate of Suitability (Ph Eur monograph)
CHMP	Committee for Medicinal Products for Human Use (formally, Committee for Proprietary Medicinal 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 Council for Harmonisation (of Technical Requirements for Registration of Pharmaceuticals for Human Use)
IPD	Individual Patient Data
IPI	Inactive Pharmaceutical Ingredient
IT	Information technology
PDF	portable document format
P&A	Pharmaceutical and Analytical
PI	Professional Information
PIL	Patient Information Leaflet
PMF	Plasma Master File
SARG	South African Regulatory Guidelines
SPC	Summary of Product Characteristics (European)
MCC	Medicines Control Council
UK	United Kingdom
USA	United States of America

INTRODUCTION

This guideline provides recommendations for applicants preparing a Common Technical Document for the Registration of Medicines (CTD) for submission to the South African Health Products Regulatory Authority (SAHPRA). The document describes how to organise applications based on the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines on the CTD. The CTD is currently only applicable to human, not veterinary, medicines.

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 *South African CTD Module 1: Administrative Information* as Module 1 is region specific.

The European *Notice to Applicants: Medicinal products for human use. Volume 2B: Presentation and format of the dossier CTD* (July 2003) 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 *South African Regulatory Guidelines (SARG)* 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 included as 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.

This guideline should be read together with the General Information guideline.

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 GCP compliance.

In cases concerning well-known active pharmaceutical ingredients, SAHPRA may grant exemption from the submission of Non-clinical and Clinical Overviews and Summaries (2.4, 2.5, 2.6 and 2.7).

Module 3 – Quality

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

Refer to the Pharmaceutical & Analytical guideline for the current requirements for this module.

Full reports on biopharmaceutic 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.
In cases concerning well-known active pharmaceutical ingredients, SAHPRA may grant exemption from the submission of Non-clinical study reports in Module 4.

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 South Africa, the sponsor should consider submitting studies relevant to those target populations.

In cases concerning well-known active pharmaceutical ingredients, SAHPRA may grant exemption from the submission of Clinical study reports, other than bioequivalence study reports, in Module 5.

European Union 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.

PART A: GENERAL INFORMATION FOR APPLICATIONS

Please read together with the General Information 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.

Refer to the ICH eCTD Specification current version and the Guidance for Submission of Regulatory Information in eCTD format regarding format and requirements for electronic submissions.

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 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 letter of application (section 1.0 of Module 1).

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

Each PART or Sub-PART should contain a Table of Contents complying with 3.1.2 above.

The items listed in the TOC should include at least all the relevant aspects addressed in the registration guidelines and/or the narrative headings of the CTD where relevant.

2 Documentation

2.1 Electronic submissions

More information about electronic lodgement will be provided on the SAHPRA website when available.

The actual submission of the physical medium/a on which the application is contained should be accompanied by at least a signed, paper copy of the letter of application (the content of this letter is defined in the ICH eCTD Specification Document Appendix 5, as is the packaging of the media units).

Refer also to 3.5 of *2.23 Submission in eCTD format.*

2.2 Paper submissions

Set 1 – Full dossier

One complete application for registration dossier and the following:

- Screening (validation) fee or proof of payment in terms of Guideline 17.01 (proof of payment must be included in section 1.2.2.1 of Module 1) *(please do not include the application fee with the screening fee*)
- Sample and copy of the sample's API and final product release certificates of analysis

  The copy of the sample's API and final product release certificates of analysis should be included in section 1.7.10.3)

On completion of administrative screening the following:

- Original letter of application for final submission must be included in section 1.0 of Module 1 (this date becomes the date of application and must be amended in Module 1.2.1)
- All administrative screening outcome correspondence as well as the Screening (validation) template with section A.2/3 also completed (Module 1.8)

- Application fee or proof of payment in terms of Guideline 17.01 (proof of payment must be included in section 1.2.2.1 of Module 1)
- The number of copies of sets requested by SAHPRA

2.2.1 Composition of copy sets

Only the information indicated should be included in each set. If sub-modules are not specifically singled out, a module implies all the sub-modules included under that section.
For instance, Module "1.7" implies Modules 1.7.1 to 1.7.13.

The sets have to be compiled in the chronological order of the CTD.

The application for registration should be properly bound on the left side as this allows for easy update/addition of pages. The left margin of documents should be wide enough to allow for legibility after copying and binding.

Binding is left to the discretion of the applicant; however, the use of lever-arch files and ring binders is not accepted and the use of metal fasteners should be avoided regardless of the thickness of the document, as they injure and damage. The binding should enable the easy handling and evaluation of documents without it coming apart. The dossier should, therefore, be bound in units not exceeding 4 cm, including the binder, also depending on the binder used.

Proof of payment should be submitted in a separate envelope attached to a copy of the letter of application.

The requirements with regard to metrication in accordance with the Legal Metrology Act should be applied in all documentation prepared locally, e.g. the professional information, patient information leaflet, label, regional modules.

Set no. and purpose	CTD
All sets, excl set 4	Completed Screening template SA.
	Module 1.8 Completed Screening template SA Details of compliance with Screening outcomes
2 P&A	Module 1.0 Letter of application
	Module 1.2.1 Application form Module 1.2.2 Annexes (1 to 8) Module 1.7 GMP
	Module 1.1 Comprehensive table of contents
	Module 1.3 PI, PIL, Labels i.e. 1.3.1.1, 1.3.2, 1.3.3
	Module 1.10 Foreign regulatory status Module 1.5.1 Literature based submissions & 3.2.R.1.4.2
	Module 2.3 Quality Overall Summary Module 1.4 Information about the experts
	Module 3 Quality
3 Names and Scheduling & Clinical generic	Module 1.0 Letter of application
	Module 1.2.1 Application form
	Module 1.3 PI, PIL, Labels i.e. 1.3.1.1, 1.3.1.2, 1.3.2, 1.3.3 Module 1.5.3 Proprietary name applications and changes, if relevant
	Module 3.2.P.1 Description and composition of the pharmaceutical product

Set no. and purpose	CTD
4 Medicines Register	Module 1.0 Letter of application Module 1.2.1 Application form Module 1.3 PI, PIL, Labels i.e. 1.3.1.1, 1.3.2, 1.3.3 Module 3.2.P.1 Description and composition of the pharmaceutical product Module 3.2.P.3.1 Manufacturers Module 1.7.4 Release
5 Scheduling NCE	Module 1.0 Letter of application Modules 1.2.1, 1.3 and 3.2.P.1 Module 2.4 Non-clinical Overview Module 2.5 Clinical Overview
6 Clinical AMRP	Module 1.0 Letter of application Modules 1.2.1, 1.1, 1.3, and 1.10 Module 1.9 Individual patient data; statement of availability Modules 1.4, 2.4, 2.5 Module 2.6 Non-clinical Written and Tabulated Summaries Module 2.7 Clinical Summary
7 Clinical & Biological	Module 1.0 Letter of application Modules 1.2.1, 1.1, 1.3, 1.8 and 1.10 Module 1.4 Information about the experts Modules 2.4, 2.5 Module 2.6 Non-clinical Written and Tabulated Summaries Module 2.7 Clinical Summary Module 3.2.P.1 Modules 4 and 5
8 Biostudy or other	Module 1.0 Letter of application Module 1.9 Individual patient data - statement of availability Module 1.11 Bioequivalence trial information Module 1.2.1 Application form Module 1.2.2 Annexes (1 to 8) Module 1.7 GMP Module 1.1 Module 1.3 i.e. 1.3.1.1, 1.3.2, 1.3.3 Module 1.10 Modules 2.3, 1.4 Module 3 Quality, including complete Module 3.2.R and Module 3.2.A Module 2.5 if applicable Module 5

For easy reference the following alternative format of the above table is given below:

	SETS							
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**
ZA CTD (MODULES)	***Submission***	***P+A***	***Names Scheduling & Clinical generic***	***Register Medicine***	***Scheduling NCE***	***Clinical AMRP***	***Clinical & Biological***	***BA BE or Other***
1.0	Full dossier, sample and payment (refer 2.2)	X	X	X	X	X	X	X
1.2.2.1		X						X
1.7.10.1		X						X
1.7.10.3		X						X
3.2.R.7		X						X
-								X
1.7								X
1.9						X	X	X
1.8		X	X		X	X	X	X
1.2.1		X	X	X	X	X	X	X
1.2.2		X						X
3.2.A								X
1.1		X				X	X	X
1.3					X	X	X	
1.3.1.1, 1.3.2, 1.3.3, 1.5.3		X	X	X	X	X	X	X
1.10		X				X	X	X
1.4		X				X	X	X
2.1		X						X
2.2		X			X	X	X	X
1.5.1		X						
3.2.R.1.4.2		X						
1.11								X
3.2.R Complete		X						X
-					X			
2.3		X						X
2.4					X	X	X	
2.5					X	X	X	[X][1]
2.6					X	X	X	
2.7					X	X	X	

	SETS							
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**
ZA CTD (MODULES)	***Submission***	***P+A***	***Names Scheduling & Clinical generic***	***Register Medicine***	***Scheduling NCE***	***Clinical AMRP***	***Clinical & Biological***	***BA BE or Other***
3.1		X						X
3.2.S		X						X
3.2.R.2		X						X
3.2.R.3		X						X
3.2.R.6		X						X
3.2.R.7		X						X
3.2.P.1		X	X	X	X		X	X
3.2.S.4 (FPP manufacturer)		X						X
3.2.S.5 (FPP manufacturer)		X						X
3.2.P.4		X						X
3.2.P.7		X						X
3.2.P.3		X						X
				X				
3.2.P.3.1 [3]				X				
3.2.R.4		X						X
1.7		X						X
3.2.P.5		X						X
				X				
1.7.4 [3]				X				
3.2.P.8		X						X
3.2.P.2		X						X
3.2.A		X					X	X
4							X	
5							X	[X][1]
1.9							X	X

2.2.1 Composition of copy sets - continued

NOTES:

1. If applicable
2. *Only* if more than one site is involved where sites are linked to specific processes and 3Fb) if more than one site is involved and sites are linked to specific processes i.e. is more detailed than in PART 1Ab)
3. *Only* if more than one site is involved where sites are linked to specific processes and 1.7.4 if more than one site is involved and sites are linked to specific processes i.e. is more detailed than in Module 1.2.1.

2.2.2 Number of copies of sets required

	Screening	*P+A*	*Names Scheduling & Clinical generic*	*Medicine Register*	*Scheduling NCE*	*Clinical AMRP*	*Clinical*	*BA BE or Other*
SET	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
New Chemical Entity medicines	1	3	3	1	1	-	1	-
New Chemical Entity Biological medicines	1	6	3	1	1	-	3	-
Medicines with Pre-clinical & Clinical data	1	3	3	1	-	-	1	-
Biological Medicines with Pre-clinical & Clinical data	1	6	3	1	-	-	3	-
AMRP	1	3	3	1	-	1	-	-
AMRP if NCE	1	3	3	1	1	1	-	-
Medicines with dissolution or other data (including solutions & injections)	1	-	3	1	-	-	-	3
Medicines with biostudy(ies)	1	2	3	1	-	-	-	2

3 Organising documents

Documents can be combined in volumes as long as they are separated by appropriately named tab identifiers. For example, the Professional Information 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.1 of 6.
- The total number of volumes of the whole application must also be indicated
- Copy number: The copies of Modules 1, 2 and 3 should 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 - Quality
2. – Body of data
P. – Product
4. – Control of excipients

- 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.

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, the letter of application (Module 1.0), Module 1.3 South African labelling and packaging (1.3.1.1, 1.3.2, 1.3.3), and Module 1.5.5 Clinical Professional Information and Patient Information Leaflet amendments / updates 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 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, photo's 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	1.2.2.1
			1.2.2.2
			1.2.2.3
			1.2.2.4
			1.2.2.5
			1.2.2.6
			1.2.2.7
			1.2.2.8
	1.3	1.3.1	1.3.1.1
			1.3.1.2
		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
		1.5.3	
		1.5.4	
		1.5.5	
	1.6	1.6.1	
		1.6.2	
	1.7	1.7.1	
		1.7.2	
		1.7.3	
		1.7.4	1.7.4.1
			1.7.4.2
			1.7.4.3
			1.7.4.4
		1.7.5	
		1.7.6	
		1.7.7	
		1.7.8	
		1.7.9	
		1.7.10	1.7.10.1
			1.7.10.2
			1.7.10.3
		1.7.11	
		1.7.12	
		1.7.13	
	1.8		
	1.9		
	1.10	1.10.1	
		1.10.2	
		1.10.3	
		1.10.4	
	1.11		
	1.12		
	1.13		

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 Letter of Application

Documentation		
1.	1.0	Letter of Application

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

At least the following should be addressed in the letter of application:

- If the application is being submitted simultaneously with one or more additional applications for the identical product this should be stated and also confirmed that the submissions are identical except for the proprietary name.
- If the dossier has been licensed in from a third party and the third party's name or logo is included in documents in the dossier, an explanation should be provided in the letter of application to clarify the relationship between the third party and the applicant.
- Clarification if the proprietary name in the original dossier (e.g. where a product has been licensed in) differs from the proposed proprietary name included in the application for registration.
- If relevant, justification for empty sections in Module 1 is to be provided in the letter of application.

For further submissions during the registration process or post-registration amendments the letter of application must be included here.

If replying to a letter from the Authority, a copy of this letter must be included here.

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

Documentation		
1.	1.2.1	Application Form
2.	1.2.2	Annexes to the application form

1.2.1 Application form

An application to register a prescription medicine for human use in South Africa must be accompanied by a completed application form[3]. The paper application form is available on the SAHPRA website [4]. The application form must also be submitted with every response to an Authority recommendation and/or an application for amendment of the dossier, including PI amendments. The footer of the document may not be changed. Section f) "Amendment history" has to be completed with each subsequent amendment.

In addition to the paper dossier, Module 1.2.1 should be submitted electronically on CD or DVD in MS Word format. A statement must be included in the letter of application to confirm that the CD/DVD is closed and the submission is checked with an up-to-date and state-of-the art virus checker: [name of the antivirus software and version of the virus checker] and is virus-free.

Note that the "Date of registration" is not applicable to "Old Medicines" (a medicine the registration of which has been applied for in terms of section 14 (3) of the Act).

a) "Business address" in relation to a business that is carried on in the Republic of South Africa, means the full physical address of the premises where such business is conducted.

b) Pharmacist responsible/authorised to communicate with Authority. Refer to Regulation 16(2) of the Act.

c) Category. Refer to Regulation 9 of the Act.

d) "Proprietary name" means the name that is unique to a particular medicine and by which it is generally identified and which, in the case of a registered medicine, is the name approved in terms of Section 15 (4) of the Act in respect of such medicine.

e) Pharmacological classification. Refer to Schedule 1 Annexure to the Regulations

f) Dosage form: Select the most appropriate dosage form from this list, when completing the administrative data. This dosage form will also be reflected on the medicine registration certificate. Specify/qualify the type of tablet e.g. chew tablet, slow release tablet, uncoated, film-coated, sugar-coated, enteric-coated, dispersible tablet.

Blood bag	Gel	Pessary
Bone cement	Globule	Plaster
Beads	Granules	Pods
Caplets	Gum	Powder
Capsules (specify type, e.g. hard gelatine, soft gelatine, modified release)	Implant	Shampoo
	Infusion (parenteral)	Soap
	Inhaler	Solution
Cleansing bar	Injection	Sponge
Combination of dosage forms	Insert	Spray
Condom	Intra-uterine device	Stick
Cone	Jam	Suppository

[3] South African Module 1.2.1

[4] www.sahpra.org.za

Cord	Leaves	Suspension
Cream	Liquid	Swab
Cardioplegic solution	Lotion	Syrup
Chip (dental)	Lozenge	Tablet *(specify e.g. uncoated or film, sugar or enteric coated; chew, dispersible)*
Decoction	Lump	
Dialysate	Medical device	
Diluent for injection	Mouthwash	Tampon
Dental material	Nasal inhaler	Test kit
Dressing	Nasal spray	Tincture
Drops	Oil	Toothpaste
Elixir	Ointment	Towelette
Emulsion	Ovule	Transdermal therapeutic system
Enema	Paste	
Foam	Pellet	Vaginal ring
Gas		Wafer

g) 'Approved name' in relation to a medicine means the internationally recognised name of such medicine, or such other name as the Authority may determine, not being a brand name or trade name registered in terms of the Trade Marks Act, 1963 (Act 62 of 1963). (Defined in Section 1 of the Act.)

h) The descriptive name of biological medicine, e.g. viral vaccine, viral antiserum, bacterial vaccine, bacterial antiserum, allergen, immunoglobulin or blood product, as given in a recognised pharmacopoeia or where such name does not exist, a name determined by the Authority.

i) The country of origin, i.e. the country where the original development was done. If development took place in more than one country, all the countries should be specified.

j) FPRR should be vested in a person who has appropriate knowledge of the relevant aspects of the medicine and who is either the holder of the certificate of registration or is in the employment of the holder of such a certificate.

k) All subsequent responses to Authority recommendations and resolutions must include a valid declaration that the response and information submitted is true, correct and relevant, i.e. Module 1.2.1 must be duly completed, dated and signed for each response.

1.2.2 Annexes to the application form

1.2.2	1.2.2.1	Proof of payment
	1.2.2.2	Letter of authorisation for communication on behalf of the applicant/PHCR
	1.2.2.3	Dossier product batch information
	1.2.2.4	Electronic copy declaration
	1.2.2.5	Curriculum vitae of the qualified person for pharmacovigilance
	1.2.2.6	API change control
	1.2.2.7	EMA certificate for a Vaccine Antigen Master File (VAMF)
	1.2.2.8	EMA certificate for a Plasma Master File (PMF)

1.2.2.1 Proof of payment

Include a copy of the proof of electronic payment. For the various fees, refer to the latest Government Gazette in this regard, as well as Guideline 17.02 bank details, 9.33 Payments

1.2.2.2 Letter of authorisation for communication on behalf of the applicant/PHCR

The application must be signed by the pharmacist responsible for the compilation of 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).

Note that such a letter is not required for the Responsible Pharmacist if the Responsible Pharmacist signs the application.

1.2.2.3 Dossier product batch information

The following are particulars which clarify the pharmaceutical development of the dosage form, from which data furnished in the undermentioned Modules were derived:

	3.2.P.3	3.2.P.5	3.2.P.8	3.2.R.1	
	Manufacture	Control of final pharmaceutical product	Stability	Bioequivalence	Dissolution
1. *Types of batches					
2. Lot number/s					
3. Lot size/s					
4. Date/s of manufacture					
5. Site/s of FPP manufacture					
6. Formulation and manufacturing process as applied for (Y/N) (clarify if not)					
7.** Site 1 of API 1					
8. Site 2 of API 1					
9.** Site 1 of API 2					
10. Site 2 of API 2					

* Experimental, pilot or production

** Add as many rows as necessary for APIs and API manufacturing sites

1.2.2.4 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-ROM/DVD have to be declared identical to that in the paper submission. The specific documents submitted in hard copy as well as digital format have to be indicated.

When electronic dossiers are supplied to replace approved paper dossiers, applicants must submit an affidavit in which they confirm that the data on the CD-ROM/DVD supplied is identical to that in the written submission.

1.2.2.5 Curriculum vitae of the qualified person responsible for pharmacovigilance

Include a curriculum vitae of the qualified person responsible for pharmacovigilance.

1.2.2.6 API change control

A formal agreement exists between the applicant of the medicine and each manufacturer of the active pharmaceutical ingredient (API) which ensures that information will be communicated between them and to the Authority 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 Authority'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 destined to be distributed in South Africa before written approval is granted by SAHPRA. Both parties understand that the consequences of failure to obtain approval for changes where approval is necessary may include de-registration and recall of batches of medicines containing this material in South Africa.

1.2.2.7 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.

1.2.2.8 EMA certificate for a Plasma Master File (PMF)

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

Module 1.3 South African labelling and packaging

Documentation	
1.3.1	South African Professional Information
1.3.1.1	Professional Information
1.3.1.2	Standard References
1.3.2	Patient Information Leaflet
1.3.3	Labels
1.3.4	Braille

Applicants should include the proposed or approved texts of Professional Information (PI) (Module 1.3.1) and Patient Information leaflet (PIL) (Module 1.3.2). South African specific labels should be submitted in Module 1.3.3 (mock-ups, specimens or text).

1.3.1 South African Professional Information

1.3.1.1 Professional Information

Module 1.3.1.1 should include a copy of the South African PI - either the proposed PI in the case of a new application, or the currently approved PI in the case of amendments. The PI shall comply with Regulation 11 of the Act, the requirements of the General Information Guideline, the Professional Information Guideline and any class labelling requirements that may be issued by the MCC from time to time.

For professional information amendments, these should be submitted in accordance with the Professional Information Guideline. See also Module 1.5.5

1.3.1.2 Standard References

Refer to the Professional Information Guideline for requirements in terms of standard references.

1.3.2 South African Patient Information Leaflet

Module 1.3.2 should contain a copy of the proposed or approved South African consumer medicine information, also known as *Patient Information Leaflet (PIL)*.

For details of the format and content see Regulation 12 of the Act and the PIL Guideline.

1.3.3 Labels

Regulation 10 of the Act must be complied with unless otherwise exempted.

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 Module 1.3.3.

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.

1.3.3 Labels - continued

If there are multiple strengths and/or pack sizes, one representative specimen or mock-up will be sufficient. If the batch number and expiry date are to be printed on the label during packaging, a statement to this effect should accompany the labels. If mock-ups or specimens are not available at the time of initial application, a text version may be submitted.

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, SAHPRA 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	Literature based submissions
	1.5.2	Amendments / Variations
	1.5.2.1	Tabulated schedule of amendments
	1.5.2.2	Medicines Register Details
	1.5.2.3	Affidavit by Responsible Pharmacist
2.	1.5.3	Proprietary name applications and changes
3.	1.5.4	Genetically modified organisms (GMO)
4	1.5.5	Professional Information and Patient Information Leaflet amendments / updates

1.5.1 Literature based submissions

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 General Information Guideline and Biostudies Guideline[5].

For professional information amendments, refer to the Package Insert Guideline.

1.5.2 Amendments / Variations

1.5.2.1 Tabulated schedule of amendments (refer to Amendments Guideline)

1.5.2.2 Medicines Register Details

1.5.2.2.1 Medicines Register Details (Appendix A1 of the Amendments Guideline)

1.5.2.2.2 Registration certificate
Include original or certified copy of registration certificate.

1.5.2.3 Affidavit by Responsible Pharmacist (Appendix A2 of the Amendments Guideline)

1.5.3 Proprietary name applications and changes

Submit a letter with details on the current and proposed names and the reason for the change in Module 1.0.

Include any information in support of a proposed name or alternative proposed names in this section 1.5.3

Changing of the proprietary name during the evaluation and registration phase will only be permitted if the the Authority has not accepted the name originally proposed by the HCR/applicant.

The policy on proprietary names is detailed in a separate guideline and detailed requirements can be found in the Amendments Guideline[6].

Proof of payment must be filed under 1.2.2.1

1.5.4 Genetically modified organisms

Genetically modified organism (GMO) means an organism in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination.

1.5.5 Professional Information and Patient Information Leaflet amendments / updates

Include annotated PI / PIL for any proposed amendments to an approved PI / PIL.
When updating or amending clinical aspects of the PI/PIL, the Storage Instructions should be updated to reflect the currently accepted wording. Refer to the Amendments guideline.

[5] www.sahpra.org.za
[6] www.sahpra.org.za

Module 1.6 Environmental risk assessment

For future use.

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 or a copy of the appropriate licence
4.	1.7.4	Release
	1.7.4.1	API
	1.7.4.2	IPIs
	1.7.4.3	Finished Product Release Control (FPRC) tests
	1.7.4.4	Finished Product Release Responsibility (FPRR) criteria
5.	1.7.5	Confirmation of contract
6.	1.7.6	CPP (WHO certification scheme) if applicable
7.	1.7.7	SAPC registration
8.	1.7.8	Registration with the Registrar of Companies
9.	1.7.9	Other documents relating to the Applicant/HCR
10.	1.7.10	Sample and Documents
	1.7.10.1	Confirmation of submission of the sample
	1.7.10.2	BMR of the sample (or refer to 3.2.R.8, or confirm available for inspection)
	1.7.10.3	CoA of sample (final product and API used)
11.	1.7.11	Certified copy of permit to manufacture S5, S6, S7 and S8 substances
12.	1.7.12	Inspection flow diagram
13.	1.7.13	Organogram

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 SA Guide to GMP).[7]

1.7.1 Date of last inspection of each site

The applicant should provide a list of manufacturers', packers' and FPRCs' names and licence numbers, with a list of the dates of inspection by the Health Authorities of either SA, FDA, MHRA, TGA, EU, Canada, PIC/S country, at each site.

[7] www.sahpra.org.za

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 Health Authorities of either SA, FDA, MHRA, TGA, EU, Canada, PIC/S country, at each site.

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/s and FPRCs or a copy of the appropriate licence.

1.7.4 Release

1.7.4.1 API

The following minimum requirement should be confirmed and the name and physical address of the laboratory(ies) performing the tests stated:

a) Identification and assay of the API will be performed by the product manufacturer irrespective of the possession of a CoA from the API manufacturer.
b) Any tests included in the specifications and not included in a valid CoA will be performed.

1.7.4.2 IPIs

(1) The following minimum requirement should be confirmed and the name and physical address of the laboratory(ies) performing the tests stated:
   a) Identification of the IPI will be performed irrespective of the possession of a CoA from the supplier.
   b) Any tests included in the specifications and not included in a valid CoA will be performed.

(2) For IPIs for which a conclusive identification test is not described, all parameters that are specific to the identification of such ingredients should be listed and the tests performed irrespective of the possession of a CoA from the supplier.

1.7.4.3 Finished Product Release Control (FPRC) tests

For imported products at least the identification and assay of the API content should be performed by an approved laboratory (FPRC) after importation. This is to verify that the product has not been affected adversely during transportation. Exemption from this requirement may be applied for according to the Post-Importation Testing of Medicines guideline.

1.7.4.4 Finished Product Release Responsibility (FPRR) criteria

The final non-analytical release criteria should include the verification of the appearance of the dosage form, the container, the professional information, the label, the batch number, the expiry date of the product, the certificate of analysis (including re-analysis for imported products) and the batch release documents (batch manufacturing record compliance) (Final Product Release Responsibility or FPRR functions).

1.7.5 Confirmation of contract

The applicant should include a signed declaration that contracts with all third party manufacturer/s and/or packer/s and FPRC/s are in place, and these should be available for inspection purposes.

1.7.6 CPP (WHO certification scheme) (if applicable)

This is the information required by the Inspectorate.

1.7.7 SAPC registration

1.7.7.1 Proof of current registration of the Responsible Pharmacist by the SAPC

Submit a copy of the South African Pharmacy Council Registration certificate of the responsible pharmacist and also proof of current registration (registration card).

1.7.7.2 Proof of current registration by the SAPC of the pharmacist signing the dossier

Submit a copy of the South African Pharmacy Council Registration certificate of the pharmacist signing the dossier and also proof of current registration (registration card), if different from the Responsible Pharmacist.

1.7.7.3 Proof of registration of the Applicant/PHCR as a pharmacy or a pharmacist

Submit a copy of the certificate of registration as proof of the SAPC Registration of the Applicant/PHCR as a pharmacy or pharmacist (read with General information Guideline[8]).

1.7.8 Registration with the Registrar of Companies

Submit a copy of the certificate of registration of the company with the Registrar of Companies (if relevant).

1.7.9 Other documents relating to the Applicant/PHCR

1.7.9.1 Letters of cession and acceptance

When an application for transfer of applicancy is submitted, include the letter of cession from the current applicant (HCR) and letter of acceptance from the proposed applicant (PHCR) here.

1.7.9.2 Company letterheads

When an application for transfer of applicancy is submitted, or the name of the applicant or address is changed, include the old and new company letterheads here.

1.7.10 Sample and Documents

1.7.10.1 Confirmation of submission of a sample: All medicine applications for registration must include a sample of a unit pack, Section 15(1) of the Act. One sample of the smallest pack size must be submitted.

1.7.10.2 Batch manufacturing record of the sample

a) included in Module 3.2.R.7 or

b) available for inspection

1.7.10.3 CoA of the sample

Include the CoA of the FPP and of the API used in the sample. Ensure that the batch number on the CoA corresponds with the batch number on the sample.

1.7.11 Certified copy of a permit to manufacture specified Schedule 5, Schedules 6, 7 and 8 substances

Include a duly certified permit to manufactured Schedule 5 (specified list), Schedules 6, 7 and 8 substances.

1.7.12 Inspection flow diagram

Submit the Inspection flow diagram, also of FPP intermediates, clearly indicating the sites and processes, including clear distinction between primary and secondary packers.
Ensure that all role players are filled in and that final release for distribution is an FPRR function.

1.7.13 Organogram

Include the current company organogram, reflecting the Responsible Pharmacist and other key responsibilities.

[8] http://www.sahpra.org.za

Module 1.8 Details of compliance with screening outcomes

Documentation:	
1.	Details of compliance with screening outcomes
2.	Details of any additional data submitted

Address the screening comments and, where documentation is involved, only provide an overview of the relevant documentation submitted. Applicants should not modify the overall organisation of the CTD; amended modules must be filed under the appropriate CTD section.

A copy of the completed screening template must be included in module 1.8, with the original completed form being submitted separately with the application.

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

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 non-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.

The individual patient data, may be requested during the evaluation period and, if a request for these data is not met within 15 working days, the application will usually lapse. Individual patient data may be requested by SAHPRA:

- 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.

If a marketing application for the medicine has been rejected in the USA, UK, Sweden, Australia, Canada, EU, or Japan, before or during the South African evaluation process, for reasons related to the clinical data in any way, full individual patient data must always be available and may be required to be submitted in South Africa. In the event that the South African evaluation process has commenced, applicants should contact the Registrar of Medicines.

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
	1.10.2	Registration certificates or marketing authorisation
	1.10.3	Foreign prescribing and patient information
	1.10.4	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

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 in South Africa has been submitted, dates of submission (if available). This should detail approvals (with indications).

Applicants must declare whether a marketing application for the medicine has been rejected in the countries listed under 1.10.1 prior to submission of the application in South Africa. If the medicine has been rejected, repeatedly deferred or withdrawn, then SAHPRA must be informed and the reasons supplied.

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 Registration certificates or marketing authorisation

In the case of registration in the country of origin, or where a marketing authorisation has been granted by the health authority of a country with which SAHPRA aligns itself, copies of the registration certificates or marketing authorisation should be supplied in Module 1.10.2.

1.10.3 Foreign prescribing and patient information

In the case of marketing authorisations in country of origin, or where marketing authorisation has been granted by the health authority of a country with which SAHPRA aligns itself, copies of relevant prescribing and patient information should be supplied in Module 1.10.3, e.g. the Canadian Product Monograph, the Summary of Product Characteristics (SPC) in the EU, UK, and Sweden, Prescribing Information (PI) in USA. If the overseas SPC, monograph or PI has not been approved at the time the application is lodged in South Africa, a draft document may be included. The approved overseas SPC, monograph or PI should then be supplied to the MCC as they become available.

SAHPRA aligns itself with a regulatory authority which is

(1) a member of the International Council for Harmonization of Technical requirements for Registration of Pharmaceuticals for Human use (ICH) i.e.
USA (FDA), European Union (EMA and National Regulatory Authorities), and Japan (MWH).

(2) an ICH observer, i.e. Switzerland (Swissmedic) and Canada (Health Canada) or

(3) a regulatory authority associated with an ICH regulatory authority member through a legally binding mutual recognition agreement i.e. Australia (TGA), Norway, Iceland and Liechtenstein.

(4) a member of the PIC/S (Pharmaceutical Inspection Co-operation Scheme) for quality matters relating to GMP.

1.10.4 Data set similarities

Module 1.10.4 should contain a summary of the similarities / differences in the data packages submitted in other countries.

Module 1.11 Bioequivalence trial information

Documentation		
1.	1.11.1	Study Title(s) (or brief description giving design, duration, dose and subject population of each study)
	1.11.2	Protocol and study numbers
	1.11.3	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
	1.11.4	Confirmation that the test product formulation and manufacturing process is that being applied for
	1.11.5	Proof of procurement of the biostudy reference product (may include cross-reference to 3.2.R.1)
	1.11.6	Name and address of the Research Organisation(s) / Contract Research Organisation(s) where the bioequivalence studies were conducted
	1.11.7	Sponsor and responsible sponsor representative: name and address, contact details
	1.11.8	Duration of Clinical phase: dates of dosing and last clinical procedure
	1.11.9	Date of final report

South Africa's requirements for biopharmaceutic studies are described in the Biostudies Guideline[9].
The Biostudies guideline is based to a large extent on the CHMP *Note for Guidance of Bioavailability and Bioequivalence* (CPMP/EWP/QWP/1401/98)22 and the relevant WHO guidelines e.g. TSR Annexes 7, 8 and 9. It also takes into account relevant FDA guidelines.

In relation to the content of biopharmaceutic study reports, this guideline states that: The report of a bioavailability or bioequivalence study should give the complete documentation of its protocol, conduct and evaluation complying with GCP rules.

SAHPRA considers it essential that the principal investigator(s) sign the study reports after their completion, either in an unqualified fashion or clearly taking responsibility for all aspects of the conduct of the study for which they might reasonably be held responsible. If the signature of the principal investigator is absent from the report of a bioavailability or bioequivalence study, it will be requested by the Authority during the evaluation process.

If an applicant wishes to justify not providing a biopharmaceutic study, Guideline P&A CTD provides a minimum set of issues to be addressed in any justification.

[9] sahpra.org.za

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 Risk management plan

For future use.

ZA CTD MODULE 1.7.12

INSPECTION FLOW DIAGRAM OF MANUFACTURED PRODUCTS

PRODUCT DETAILS

Product Name :

Reg. no. :

PHCR/Applicant :

Dosage form :

Strength(s) :

Pack sizes(s) :

LOCATION

A :

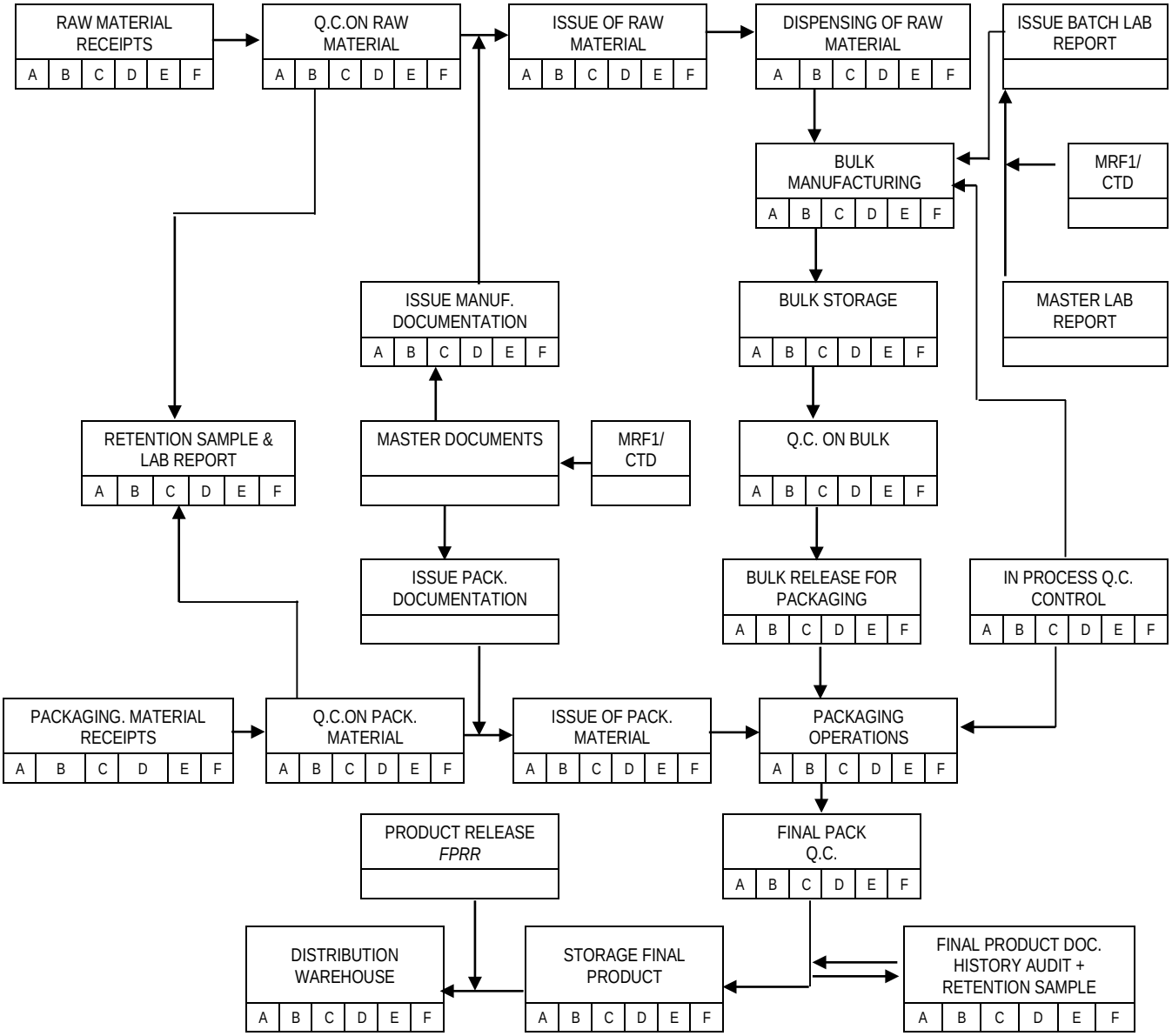
B :

C :

D :

E :

F :



UPDATE HISTORY

Date	Reason for update	Version & publication
Nov 2009	First publication released for implementation and comment	Version 1, Dec 2009
June 2010	Release for implementation and comment	Version 2, June 2010
1 July 2010	Date of implementation	
30 September 2010	Due date for comment	
March 2011	Renamed guideline and amended in line with amendments to ZA CTD	Version 3, March 2011
	Amendment of Abbreviations, Introduction, and PART A sections 1, 2.2, 2.2.1; 2.2.2, 7, 8	
	Amendment of PART B – Module: 1.0, 1.2.1, 1.2.2, 1.2.2.2, 1.2.2.4, 1.2.2.6, 1.2.2.7, 1.2.2.8; 1.3 –1.3.1, 1.3.2; 1.4; 1.5 – 1.5.2, 1.5.5; 1.7 – 1.7.1, 1.7.2, 1.7.3, 1.7.5, 1.7.6, 1.7.7, 1.7.8, 1.7.9, 1.7.10, 1.7.11 (deleted), 1.7.13 now 1.7.12; 1.7.13 added; 1.10 – 1.10.1, 1.10.2, 1.10.3; 1.10.5/6 moved to 1.10.1; 1.11 – 1.11.3, 1.11.5	
1 June 2011	Date of implementation	
August 2011	Amendment of Module 1.7.7-9 to include registration with Registrar of Companies and other documents relating to the HCR; corrections under 1.3 and 1.10.1	Version 4, August 2011
With immediate effect	Date of implementation	
July 2012	Part A: 1, 2.2, 2.2.1, 2.2.2, 5, 7 Part B: 1.0, 1.3.1.1, 1.5.2, 1.5.3, 1.5.5, 1.8	Version 5 August 2012
With immediate effect	Date of implementation	
With immediate effect	Change from MCC to SAHPRA Relevant sections moved from the General Information guideline Amendments to Abbreviation & Acronyms, Introduction Part A: sections 1, 2.1, 2.2, 3, 4 Part B – Module: 1.0, 1.2.1, 1.2.2.1, 1.2.2.4, 1.2.2.6, 1.3, 1.4, 1.5, 1.7.4.4, 1.9, 1.9, 1.10, 1.11	Version 6, May 2019