South African Health Products
Regulatory Authority
Building A
Loftus Park
Arcadia
Pretoria

17 April 2023

GENERAL INFORMATION GUIDELINE

This guideline is intended to provide recommendations to applicants wishing to submit applications for the registration of medicines. It represents the South African Health Products 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. This guideline is relevant only to human medicines, including biological and complementary medicines. Separate guidelines apply to the registration of veterinary medicines, medical devices and other health products

Guidelines and application forms are available from the website www.sahpra.org.za.

Document History

Final Version	Reason for Amendment	Effective Date
1	First publication released for implementation and comment	May 2003
1	Date for finalisation / implementation	Dec 2003
2	General editing – page numbers in index, 2.5, 3.1.2, 3.1.3 a) b), 4.1, 4.4, 4.17, 8, 10, and amendment of sections 2.2.2, 2.9, 3.1.4, 4.2, 4.5, 4.6, 4.7, 4.14, 5, 5.2, 13.1, 13.2, 13,3, 13.4, 13.5, 13.6, 13.7, Attachment A	12 July 2006
3	Additions to 2.7.5, 2.10.5, 13.4; amendments to 4, 5.2, Attachment A	25 June 2007
4	Amendment of sections 2.9, 2.10.5, 3.1.3 a), 4, 4.7, 4.10, 5.1, 5.2, 13.3, 13.4, Attachment A	01 August 2008
5	Removal of section 12 "Standardised package insert warnings" and inclusion in new "Package Insert Standardised Texts" guideline Removal of Attachment B re: package insert information Amendment to section 4.9	March 2010
6	Inclusion of references to the ZA CTD – sections 2.11, 3, 4, 4.14, 5, 13.1 Amendment of section 2.5 Amendment, for clarity, of sections 2.10.5 k), 3.1.2, 3.1.3 c), 3.1.4, 3.4, 3.5, 4.3, 4.5, new 4.6, 4.9 (original 4.8), 4.10 (original 4.9), 4.17, 5.2, 5.4, 13.3, 13.9 & new section 3.1.1 p)	21 June 2010

7	Amendment of name of “Post-registration Amendments”, “Guidance for submission of SA CTD / eCTD Module 1" guidelines, and administrative amendments: Sections 2.5, 3, 3.1.1o), 4, 4.5, 5, 5.2.6, 5.2.8, 5.4, 13, 13.1, 13.2, Attachment A; new 4.11 and renumbered. Amendment of 2.2.2 for clarification & in line with CTD guideline. Clarification of 4.3 & 4.4 in accordance with Biostudies guideline 3.9 & 4.4 and insertion of 4.11 in accordance with Quality and Bioequivalence Guideline 2.1.2.11. Deletion of “independent” in 6.2 & 8.1. Insertion of “(including batch specific)” for shelf-life extension under working code VSE in accordance with Amendments guideline Type C Inspectorate category 19.	March 2011
7	13.1 Correction	June 2011
8	Deletion of section 9 on Proprietary Names, Attachment A (pre- screening checklist) Amendment of 2.11, 3.1.4, 4, 4.2, 5.2.8, 6, 13.2, 13.9	August 2012
9	Transition from MCC to SAHPRA *To include sections changed or deleted*	May 2019
10	Updated to align with new processes and guidelines	July 2019
11	New template and numbering Updated to align with new processes and guidelines Amended sections: 1.2; 3.1; 3.4; 3.6; 3.7; 3.9; 3.14; 3.15; 4; 5; 6; 7; 9; 10 Added sections: 2.5; 3.5; 3.13; 3.16; 3.17; 3.18; 3.19 Deleted information on coding of submissions Deleted reliance information in section 3.8 Deleted sections 3,10; 3,11 & 3,12	April 2023

DR BOITUMELO SEMETE-MAKOKOTLELA
CHIEF EXECUTIVE OFFICER

Contents

Glossary

Abbreviation/ Term	Meaning
API	Active Pharmaceutical Ingredient (also known as Drug Substance)
Applicant:	Organization creating and submitting the eCTD submission. Can either refer to the PHCR or HCR
Application number:	The application number is the official reference number assigned to the dossier or eCTD application by the Authority. It remains with the dossier for its full life cycle and also in archiving.
CD	Compact Disc
CD-ROM	Compact Disc Read-Only Memory
CEM	Clinical Evaluation and Management
Clone	Application submitted by the innovator as a copy of its own product under a different proprietary name at any stage during the product life cycle
CTD	Common Technical Document
Dossier:	A collection of documents compiled by an applicant in compliance with South African legislation and guidelines in order to seek registration of a medicine, or any variations thereof. An application may comprise a number of submissions.
eCTD application:	A collection of electronic documents compiled by an applicant in compliance with South African legislation and guidelines in order to seek registration of a medicine, or any amendments thereof. An eCTD application may comprise a number of eCTD Sequences. In South Africa, an eCTD application may comprise several strengths, each with a unique proprietary name. Such a collection may also be described as a dossier.
eCTD Submission:	An eCTD Submission is an electronic-only submission in the eCTD format that is supported by paper documents (e.g., some documents from Module 1).
eSubmission:	An electronic submission that follows the CTD format.
FPP	Finished Pharmaceutical Product
HCR	Holder of Certificate of Registration
HPA	Health Products Authorisation
ICH	International Council for Harmonisation (of Technical Requirements for Registration of Pharmaceuticals for Human Use)
INN	International Non-proprietary Name
IRC	Inspectorate and Regulatory Compliance
PEM	Pharmaceutical Evaluation Management
PHCR	Proposed Holder of Certificate of Registration
PI	Professional Information
PIL	Patient Information Leaflet
Q & BE	Quality and Bioequivalence
Replica	A copy of an already registered generic product, submitted by the same or by another applicant at any stage during the product life cycle.

RRA	Recognised Regulatory Authority
SCoRE	Summary of Critical Regulatory Elements
SAHPRA	South African Health Products Regulatory Authority

1. INTRODUCTION

The registration of a medicine in South Africa is governed by the provisions and requirements of the Medicines and Related Substances Act, 1965 (Act No. 101 of 1965), (hereafter 'the Act') and the regulations and guidelines published in terms thereof.

These guidelines describe the information required for the registration of “medicines” and for an application to amend a registered medicine. The information submitted will be evaluated in terms of the provisions of the Act.

Medical devices including *in vitro* diagnostics are addressed in separate guidelines.

It is a legal requirement that data submitted for evaluation should substantiate all claims and should meet technical requirements of quality, safety and efficacy of the product for the purposes for which it is intended. The guidelines are meant to guide the applicant in meeting the requirements of the Act. It is acknowledged, however, that in some instances scientific developments may dictate alternative approaches. When a deviation from a guideline is decided on, a detailed motivation giving the reason(s) for the deviation and justification for the alternative approach should be included in the expert report submitted with the application.

Whenever there is doubt, applicants are advised to consult SAHPRA for confirmation and / or clarification before completing and submitting the application form; refer to the website for contact details. Applicants should always refer to the current version of the relevant guidelines and the addenda thereto before completing the application form.

Guidelines are constantly evolving due to scientific developments and harmonisation of the requirements of regional and international regulatory authorities. SAHPRA endeavours to regularly update the guidelines to reflect current thinking and keep its technical requirements and evaluation policies in line with “best international medicines regulatory practice”.

1.1 Purpose

The aim of this guideline is to assist applicants in the preparation of documentation for the registration of medicines for human use. The types of medicine include a new medicine for a new chemical entity (NCE) including clones, a multisource (generic) product including replicas, a product line extension, a biological medicine, and a complementary medicine.

1.2 Scope

These guidelines are relevant only to human medicines including biological and complementary medicines. Separate guidelines apply to the registration of veterinary medicines (SAHPGL-PEM-VET-04 Guideline for Registration of Veterinary Medicines) and medical devices.

2. LEGAL PROVISION

Legislation requires that SAHPRA shall register every medicine before it may be sold / marketed. An application for the registration of a medicine should therefore be submitted for evaluation and approval.

3. GENERAL

3.1 Applicant / PHCR / HCR

The term 'applicant' can refer either to the proposed holder of the certificate of registration (PHCR), as in the case of a new registration, or to the holder of the certificate of registration (HCR), as in the case of a variation application. Throughout this document, the term 'applicant' is used to refer to either the PHCR or the HCR, based on whichever is applicable in the context.

Eligibility to apply for registration of a medicine is governed by Regulation 16 of the Act. An application may be made by any of the following:

a) a person, body corporate / juristic person, company, residing and doing business in South Africa;

b) a close corporation incorporated in South Africa; or

c) a company in South Africa with at least

- a responsible delegated person residing in South Africa and
- an authorised person residing in South Africa who must be a person with appropriate knowledge of all aspects of the medicine and who shall be responsible for communication with the Authority.

The application submitted should be signed by the pharmacist authorised to communicate with the Authority. This pharmacist should be in the full-time employ of the company and may be:

- the Responsible Pharmacist in terms of the Pharmacy Act, 1974 (Act 53 of 1974) as amended, or
- another registered pharmacist responsible for regulatory affairs and with appropriate knowledge of all aspects of the medicine.

The following should be included:

- proof of **current** registration (copy of certificate) of the pharmacist who signed the dossier, and
- proof of **current** registration of the Responsible Pharmacist in terms of Act 53;
- 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.)*

An applicant should submit a Site Master File (SMF) in accordance with the Site Master File Guideline SAHPGL-INSP-04. For subsequent applications, reference to the allocated SMF number will suffice.

3.2 Confidentiality /Secrecy

The confidentiality of information submitted to SAHPRA is governed by Section 34 of the Act. The Authority, advisory committee members or staff of the Authority may NOT

- disclose to any person, any information acquired in the exercise of powers or performance of functions under the Act and relating to the business affairs of any person, except
  - for the purpose of exercising his / her powers, or for the performance of his/her functions under the Act, or

- when required to do so by any competent court or under any law, or
- with the written authority of the CEO, or

- use such information for self-gain or for the benefit of his employer.

SAHPRA may insist on written confirmation of the identity and affiliation of an individual inquiring telephonically, or in person, about a medicine. No information shall be disclosed telephonically unless the Authority staff member knows the enquirer is entitled to receive the information.

3.3 Language

In terms of Regulation 16 (4) of the Act, all applications and supporting data submitted to SAHPRA should be presented in English (UK)). Original documents not in English should be accompanied by an English translation.

3.4 eCTD identifier/Application Number

Refer to the guideline 2.23 Submission of Regulatory information in eCTD format

3.5 Where to submit applications

The medium for submitting eCTD, CTD and eSubmission related submissions to the authority is through the online upload utility (refer to the SAHPGL-ICT-01_File Transfer Protocol (FTP) User Guide for Files/Dossier Submission). A request for the File Transfer Protocol (FTP) User Guide for Files/Dossier Submission should be sent to newmedicines@sahpra.org.za. An applicant seeking access to the FPT should submit a request, with a licence number, to newmedicines@sahpra.org.za.

In the event that the Online Upload Utility is inaccessible due to a natural disaster and/or the submission size exceeds the required limit as defined on the electronic submission system, USB drives (2.0 or higher) are permitted and should meet the following requirements:

The submission media should be packed adequately (in an envelope) to prevent damage to the media. All the contained media units should be appropriately labelled as described below.

An USB submitted with an eCTD should include the following label information, clearly presented and printed on the media, or attached securely to the USB drive (for example using a tag that is securely attached to the USB body)

- The applicant's name
- The proprietary name(s)
- The registration number or application number
- The International Non-proprietary Name(s) (INN) of the product
- The sequence number of the eCTD submissions contained on the USB
- The submission date (MM-YYYY)
- The submission type of each eCTD submission(s) contained on the USB, as per the eCTD envelope information.

Applications should be delivered to the SAHPRA Reception, Building A, Loftus Park, Second floor, Kirkness Road, Arcadia, Pretoria, where they will be logged and acknowledged. All correspondence should be addressed to the Chief Executive Officer.

SAHPRA will not take responsibility for applications posted or delivered to any other place or in any other manner.

HPA should be notified if applications are submitted in a manner other than the Online Upload Utility.

3.6 When a product should be registered

A product is liable for registration with SAHPRA if any of the following apply.

i) Any of the ingredients of a product is listed in one of the Schedules to the Act;

ii) The product is a medicine by virtue of the definition of a medicine in the Act. The Act defines a medicine as:

> "any substance or mixture of substances used, or purported to be suitable for use, or manufactured or sold for use in;
>
> (a) the diagnosis, treatment, mitigation, modification or prevention of disease, abnormal physical or mental state, or the symptoms thereof in man; or
>
> (b) restoring, correcting, or modifying any somatic or psychic or organic function in man; and includes any veterinary medicine."

iii) If the product falls under any of the pharmacological classifications as specified in Annexure 1 to the Regulations

iv) The intended use of a product and the text / words used in promoting the product, even if no claims are reflected on the label, render the product registerable.

The relevant provisions and guidelines shall apply to a medicine called up as a complementary medicine.

3.7 Types of applications

Medicine applications for registration for humans are divided into the following types for the determination of fees and allocation to reviewers for evaluation:

New chemical entity applications (including clones) that include **non-clinical** and **clinical** information in support of the efficacy and safety of the formulation / dosage form, indication(s) and dosage regimen.

Multisource / generic applications (including replicas) and extension applications that include:

- clinical information in support of efficacy and safety of the formulation / dosage form, or indication(s) or dosage regimen.
- comparative bioavailability / bioequivalence studies as proof of efficacy.
- comparative dissolution studies as proof of efficacy
- any other comparative studies as proof of efficacy
- others, not mentioned above e.g., liquids / solutions.

Category D Medicines: Guideline 7.03 - Use of the ZA-CTD Format in the Preparation of a Registration Application" should also be followed to determine completeness.

Data provided in applications for registration of Category D medicines should be in the latest version

of the Common Technical Document (ZA-CTD) format as published by the SAHPRA. A risk-based approach is undertaken for Category D medicines where discipline-specific medicines are considered across a range from HIGH RISK (clinical evidence required in justification of safety and efficacy) to LOW RISK (traditional evidence may be submitted in justification of safety and efficacy) based primarily on indication but also on composition and dosage form.

The Authority will in future, consider online mechanisms for the submission of applications for registration of Category D Medicines, which will continue to make use of the CTD format.

The following guidelines are relevant to the compilation of applications for registration of Complementary Medicines:

(a) Guideline 7.01 - Discipline-Specific Safety and Efficacy
(b) Guideline 7.04 - Health Supplements Safety and Efficacy
(c) Guideline 7.05 - Registration Application ZA-CTD – Quality
(d) Guideline 7.06 – Specified Substances

Biological medicines: Biopharmaceuticals and Biosimilars

Biological medicine: A medicine where the active ingredient and / or key excipients have been derived from living organisms or tissues or manufactured using a biological process. Biological medicines can be defined largely by reference to their method of manufacture (the biological process). These include *inter alia* medicines prepared from the following substrates:

(i) Microbial cultures (fermentation),
(ii) Plant or Animal Cell cultures (including those resulting from recombinant DNA/RNA or hybridoma techniques
(iii) Extraction from biological tissues; and
(iv) Propagation of live agents in embryos or animals.

The living substrate may be genetically modified in several ways to provide the required active ingredient, including recombinant DNA technology or hybridoma techniques**.**

Biological Medicines include, but may not be limited to the following:
(i) Plasma-derived products, e.g., Clotting factors, Immunosera,
(ii) Vaccines,
(iii) Biotechnology-derived medicinal products (rDNA products) e.g., rHu-antihemophilic factors, hormones, cytokines, enzymes, monoclonal antibodies, erythropoietin's,
(iv) Human Gene therapy.

It has been the practice, in South Africa, that SAHPRA will decide that certain well-characterised low- molecular weight medicinal biological compounds, such as antibiotics, insulin etc. be excluded from biological medicine status.

Biopharmaceutical: Patented biological medicine.

Biosimilar: Biological medicines that are manufactured to be similar to the registered originator/ innovator medicines.

3.8 Evaluation Pathways

Medicines applications for new registrations and variations in South Africa will follow one of four evaluation / review pathways:

i. Full review
ii. Abridged review
iii. Verified review
iv. Recognition

Full review is defined as aA comprehensive / thorough review of all aspects of the dossier, based primarily on the evaluation of data (and summaries thereof) submitted by the applicant. This is the default evaluation pathway for new registrations and variations not previously approved by SAHPRA or an RRA, or where reliance documentation provided to SAHPRA is deemed to be insufficient.

Refer to the Reliance Guideline – 5.08 for information on evaluation pathways.

3.9 SAHPRA's Recognised Regulatory Authorities

To qualify for a reliance evaluation pathway, an application must have been approved by one or more of the RRAs with which SAHPRA aligns itself. SAHPRA's current RRAs include:

- European Medicines Agency Centralised Procedure (EMA CP)
- European Medicines Agency Decentralised Procedure (EMA DCP)
- Health Canada
- The EU's Mutual Recognition Procedure (MRP)
- EU National Procedures
- Medicines and Health Products Regulatory Agency (MHRA), UK
- Ministry of Health, Labour and Welfare (MHLW)/Pharmaceutical and Medical Devices Agency (PMDA), Japan
- Swiss Agency for Therapeutic Products (Swissmedic)
- Therapeutic Goods Administration (TGA), Australia
- US Food and Drug Administration (US FDA)
- WHO listed Authorities (WLA)

The following additional procedures can be used for reliance / collaborative review, which are not strictly regulatory authorities:

- World Health Organisation Prequalification (WHO PQ)
- World Health Organisation Collaborative Registration Process (WHO CRP)
- Zazibona collaborative procedure

3.10 Expedited review process

Refer to the latest version of HPA03-202223 Priority Review Requests Communication

3.11 Medicines for Use in a Public Health Emergency (PHE)

Refer to the latest version of the guideline - SAHPGL-PEM-01 Availability of medicines for use in a PHE.

3.12 Fees

The fees payable are published in the Government Gazette and are also available on the SAHPRA website.

Refer to 17.5 Payment Guideline for the details of the payment of fees to SAHPRA.

Note:

The only valid payment evidence to be included in M1.2.2.1 should be the proof of payment from the applicant's bank.

On notification of registration, the registration fee proof of payment, from the applicant's bank, and the final, signed PI and PIL should be submitted in one email via the relevant mailbox to SAHPRA.

3.13 Same or separate applications

For the purposes of registration, the following products will be regarded as either being the same product or separate product applications:

TYPE OF APPLICATIONS	Application	
	Same	Separate
3.13.1 Each individual dosage form of a particular medicine		X
3.13.2 Variations of the active pharmaceutical ingredient (API) of a product		X
3.13.3 Tablets / Capsules / Suppositories / Lozenges		
a) Different pack-sizes of the same strength and formulation.	X	
b) Different strengths and formulations.		X
c) Uncoated and coated tablets of the same strength and formulation.		X
3.13.4 Syrups / Liquids / Solutions (excluding parenterals) / Creams / Ointments		
a) Different container sizes of the same strength and formulation.	X	
b) The same container size of different strengths and formulations.		X

TYPE OF APPLICATIONS	Application	
	Same	Separate
3.13.5 Ampoules and Vials and Large Volume Parenterals		
a) Ampoules or single dose vials containing identical solutions of the same strength but of different volumes (i.e., resulting in different total doses).		X
b) Ampoules containing solutions of different strengths.		X
c) Ampoules and single dose vials containing e.g., dry powder, crystals of different mass.		X
d) Ampoules and single dose vials containing the same respective masses of e.g., dry powder, crystals.	X	
e) Ampoules, single dose vials, as well as pre-filled disposable syringes and cartridges containing identical solutions of the same strength and same volume of liquid.	X	
f) Dental cartridges containing different volumes of fluids of the same strength (provided the dose remains constant).	X	
g) Ampoules containing "water for injection", but of different volumes.	X	
h) Special ampoules of dry powder and "water for injections" contained in the same unit but intended for mixing at the time of injection if water for injections is fully described in dossier.	X	
i) Ampoules containing identical solutions of different volumes used only as diluent in the reconstitution of a preparation for parenteral use.	X	
j) Multidose vials containing different volumes of the same strength and formulation with the same dosage schedule.	X	
k) Multidose vials and a single dose ampoule or vial of the same formulation if the single-dose ampoule or vial corresponds to the dose indicated for the multidose vial.	X	
l) Multidose vials containing dry powder of different mass of the same formulation, and the same concentration when reconstituted.	X	
m) An ampoule of diluent packed together with any preparation including biological medicines if diluent is fully described in dossier.	X	
n) Infusion solutions of the different volumes and of the same formulation which are packed in containers of exactly the same type of material depending on the relevant information submitted.	X	
o) Infusion solutions of the same formulation and of the same or different volume which are packed in containers made of different types of materials.	X	
p) A preparation, packed in plastic containers, intended to be marketed in glass containers containing the same volume and the same formulation.	X	
q) Products with the same strength and formulation but with different colours and / or flavours.		X

TYPE OF APPLICATIONS	Application	
	Same	Separate
r) Applications containing the same API(s) applying for additional indications which render the product in a different scheduling status, or different pharmacological classification, or have any other restrictions imposed other than the original application.		X
s) Removal of antimicrobial preservative from single dose presentation of registered vaccine that included a preservative in the original approved formulation		X
3.13.6 Same formulation with different proprietary names whether of the same or different applicants		X
3.13.7 Clone or Replica applications		X

3.14 Variations Permitted during the Registration Process

All applications for registration in terms of Section 15 of the Act 101 are required to be complete in terms of the eCTD and data requirements and no variations during the registration process are permissible except for the following:

3.14.1 Transfer of Applicancy with motivation in exceptional circumstances

3.14.2 Urgent restriction safety updates as requested by or as deemed necessary by SAHPRA or the applicant following consultation with SAHPRA

3.14.3 Updated reliance documentation, e.g. where an RRA approval is obtained for the product after the application was submitted to SAHPRA

3.15 Permissible review response rounds and period for response submissions

3.15.1 SAHPRA's review process for new medicines and variations will permit for all units a maximum number of three response rounds. If the applicant fails to address the queries adequately by the third query round, the application will be tabled for rejection from the respective unit.

3.15.2 Each response timeframe should be no longer than 30 working days from the date sent to the applicant

3.15.3 Applicants may submit a *written request for one extension of timeline for a response per response round and which may not exceed a further 30 working days

*A query letter should be responded to within 30 working days. Applicants may request an additional period of up to 30 working days for providing their responses in writing to the Authority outlining their reasons. This request will however only be considered by the Authority if the applicant provides appropriate scientific justification. The Authority will review the justification for the additional period (up to 30 additional working days) for responding to a query letter following receipt of the Applicant's request and will grant such request in writing to the Applicant, only in the event that it is considered that this extension will enable the Applicant to respond fully to the queries raised. Extensions beyond 60 working days from the initial date of issue of a query letter would not normally be accepted.

3.15.4 Note: If an applicant does not respond to the query referenced in 3.17.3 and does not communicate any request for extension, this application will be tabled for rejection.

3.15.5 Applicants are encouraged to respond sooner than the expected response timeline.

3.16 Renewals

Refer to the latest version of the following documents:

- *SAHPGL-HPA-04 Renewal of Human and Veterinary Medicines Requirements and Process*
- *Communication on Medicines Registration Renewals Implementation Framework*
- *Renewals Frequently Asked Questions (FAQs)*

3.17 Cancellation or Withdrawal of applications

HCRs of medicines and applicants should, before applying to the Authority, carefully consider any decision to cancel or withdraw, as the case may be, a registration or application for registration, as the Authority, after consideration of all issues involved, has resolved the following with immediate effect.

Any medicine

- of which the registration has been cancelled, or any "old medicine" of which the application for registration has been withdrawn by notice in the Government Gazette, and
- for which a written application or request has been submitted by the holder of a certificate of registration or by the applicant, to the CEO

will under no circumstances be re-instated.

Written applications or requests to cancel registrations or withdraw applications for registration should be sent to the dedicated mailbox: cancellations@sahpra.org.za

Should the applicant desire to re-register such medicine, a new application for registration of a medicine must be submitted in accordance with the requirements of the Act and the relevant Regulations.

An application for registration of a medicine may, at whatever stage of processing, be withdrawn by written application to the CEO. The withdrawal shall under no circumstances be reversed once such an application is approved and the approval confirmed in writing. A new application for registration must be submitted should the applicant wish to proceed with registration thereafter.

4. REQUIREMENTS OF AN APPLICATION

Submission of new applications in eCTD (electronic Common Technical Document) format is mandatory (excluding complementary and veterinary medicines).

Post-registration variations may be submitted in eCTD or eSubmission format. Refer to SAHPGL-HPA-05 BAU Variations Communication for more detail.

For further information on the accepted submission format and timelines for implementation of digital requirements, refer to the following guidelines

- 2.21 South African Specification for eCTD Regional - Module 1
- 2.23 Guidance for submission of regulatory information in eCTD format
- 9.127 BAU eCTD Implementation Roadmap

Specific guidelines also apply to the requirements for an application for complementary medicines.

5. PROPRIETARY NAME AND SCHEDULING OF SUBSTANCE AND MEDICINE

Refer to the current version of the Guideline for Proprietary Names for Medicines (SAHPGL-CEM-NS-03) and Guideline to the scheduling of substance and medicine (SAHPGL-CEM-NS-02)

6. MANUFACTURING REQUIREMENTS

Only medicines manufactured, packed and quality controlled at sites compliant with the current principles of Good Manufacturing Practice (GMP) as prescribed by SAHPRA will be considered for registration.

SAHPRA's general policy is that the standard to be used to assess compliance with current Good Manufacturing Practice (cGMP), is the South African Guide to Good Manufacturing Practice (SA guide to GMP) (latest edition) (SAHPGL-INSP-02)

Under Section 22C of the Act, all South African manufacturers should be licensed (effective 2 May 2004).

The aim of these licensing requirements and standards is to protect public health by ensuring that medicines meet defined standards of quality and are manufactured in conditions that are clean and free of contaminants.

The Act requires that overseas manufacturers of medicine supplied to South Africa should comply with the same or equivalent manufacturing standards as expected of South African manufacturers.

Evidence in relation to compliance with Good Manufacturing Practices of the overseas manufacturer is required for applications for registration of imported medicines. When acceptable evidence of GMP compliance is not available, overseas manufacturers are inspected by the GMP Inspectorate before registration of the medicine is approved. SAHPRA reserves the right to request additional documentation, schedule an inspection or reject any sites.

7. SAMPLES

All medicine applications for registration must include a sample of a unit pack, Section 15(1) of the Act.

Photographs of all dimensions of the sample in the final primary packaging and of the sample itself should be included in the application on submission. A sample may be requested by SAHPRA for testing and/or viewing purposes.

8. STANDARDISED PROFESSIONAL INFORMATION WARNINGS AND INFORMATION

Refer to the current version of Professional Information for Human Medicines: Standardised Texts Guideline

9. RESPONSIBILITIES OF EACH UNIT

9.1 Pharmaceutical Evaluations Management (PEM) Sub Programme 4 consists of the following sub-units

9.1.1 PEM Pre-Reg Sub-Unit also referenced as the Quality & Bioequivalence Unit (Q & BE) is responsible for the evaluation of all new registrations (small molecules) in terms of

a) Quality of the drug substance (API) and drug product (finished pharmaceutical product)

b) Bioequivalence of generic medicines to their innovator counterparts.

9.1.2 PEM Post registration Sub-Unit also referenced as the Quality & Bioequivalence (Q & BE) Variations Unit is responsible for the evaluations of variations to registered products (small molecules) in terms of

a) Quality of the drug substance (API) and drug product (finished pharmaceutical product)

b) Bioequivalence of generic medicines to their innovator counterparts.

9.1.3 The Complementary Medicines Sub-Unit is responsible for

a) evaluation and review of applications for the registration of Complementary Medicines

b) receiving and collating initial and subsequent responses

c) evaluation and review of applications for the amendment of the register for Complementary Medicines

d) issue licenses for the manufacture, imports, exports, wholesale and distribution of Complementary Medicines.

9.1.4 The Biologicals Sub-Unit is responsible for

a) biological new registration applications and responses to resolutions, and matters pertaining to biological medicines during review for registration

b) evaluation of technical changes to registered biological medicines and "old" biological medicines

c) evaluation of clinical aspects of the Professional Information and relevant changes to Professional Information for biological medicines;

d) technical support to other units with respect to biological matters.

Note: For biologicals:

- For any activities not described above, the applications and / or queries should be directed to (and properly coded for) the relevant Units.
- Relevant supportive documentation should be attached as per the Modules/Sections described in the relevant CTD format.

9.1.5 Veterinary medicines Sub-Unit

Refer to SAHPGL-PEM-VET-04 Guideline for Registration of Veterinary Medicines for information on Veterinary product applications.

9.2 Inspectorate and Regulatory Compliance (IRC) Programme 3

The Inspectorate and Regulatory Compliance is responsible for

a) inspection and evaluation of sites for the manufacturing, packing, and testing of medicines nationally and internationally, as well as inspection and evaluation of all storage and distribution sites for medicines

b) investigation of complaints regarding registered and unregistered medicines

c) monitoring compliance with the Act and prosecution in case of non-compliance

d) monitoring the importation and exportation of medicines in consultation with customs authorities

e) Licensing of manufacturers, importers and exporters of orthodox medicines

9.3 Clinical Evaluations and Management (CEM) Sub Programme 4

9.3.1 The Clinical Evaluation Unit is responsible for

a) evaluation of clinical and pre-clinical data

b) evaluation of clinical aspects of the Professional Information and relevant changes to Professional Information

c) evaluation of proprietary names and changes thereto

9.3.2 The Clinical Trials Unit is responsible for the evaluation of

a) clinical trial applications and clinical trial amendments

b) reports of adverse events arising from a clinical trial

9.4 Health Products Authorisation (HPA) Programme 2

Health Products Authorisation is responsible for the following:

a) receiving applications for registration of medicines and variations
b) certification of new registrations, applicant transfers and proprietary name changes
c) cancellations of registered medicines and withdrawal of applications for the registration of medicines
d) communication of queries to applicants

10 REFERENCES

The following related documents are referenced:

10.1 SAHPGL-CEM-01 Clinical Guideline

10.2 SAHPGL-CEM-02 Guideline for Professional Information for Human Medicines

10.3 SAHPGL-CEM-03 Guideline for Patient Information Leaflet for Human Medicines

10.4 SAHPGL-HPA-04 Renewal of Human and Veterinary Medicines Requirements and processes

10.5 SAHPGL-PEM-01 Availability of medicines in a Public Health Emergency (PHE)

10.6 9.127 eCTD Implementation Roadmap Communication

10.7 5.08 Reliance Guideline

10.8 2.23 Guideline for Submission in eCTD format

10.9 SAHPGL-HPA-03 eCTD Validation Criteria

10.10 2.21 South African Specification for eCTD Regional - Module 1

10.11 SAHPGL-PEM-02 Quality and Bioequivalence Guideline

10.12 SAHPGL-INSP-02 Guideline for Good Manufacturing Practice

10.13 17.05 Payment Guideline

11 VALIDITY

This guideline is valid for a period of 5 years from the effective date of revision and replaces the General Information Guideline, 2.01. It will be reviewed on this timeframe or as and when required.