South African Health Products
Regulatory Authority
Building A
Loftus Park
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GUIDELINES FOR POST-MARKETING SURVEILLANCE OF MEDICINES AND HEALTH PRODUCTS

To develop a medicines and health products information data bank on quality of medicines and health products in circulation and disseminate such information to stakeholders involved in the medicines and health products supply chain.
To promote communication and cooperation between stakeholders and partners involved in medicines and health products supply chain.
To identify possible causes of inferior quality of specific medicines and health products to which patients are exposed.
To determine registration status of medicines and health products on the market and to assess the quality and safety of medicines and health products on the market and conformity with acceptable specifications as published in an official Pharmacopeial monograph or registration dossiers.
To evaluate the quality of selected medicines and health products available in the market in selected areas or regions at various levels of the distribution / supply chain with the aim of assessing the exposure of patients to poor-quality medicines and health products and proposing appropriate actions.
To compare the quality of domestically produced and imported medicines and health products in order to recommend appropriate regulatory actions and adjust pharmaceutical policy.
To propose possible strategies and implementation plans to address the problems identified by the survey based on usage, dissatisfaction or adverse events reported.
To test the quality of selected medicines and health products in order to support the Authority in identification of manufacturers/importers that are not in compliance with quality standards and regulatory measures.
To combat the spread of counterfeit/substandard medicines and health products in South Africa.
To find out if, within a selected category of medicines and health products any spurious/falsely labelled/falsified/counterfeit products have penetrated the market in selected areas or regions, what the possible health impacts may be for patients, and to propose possible strategies and implementation plans to prevent harm to patients.

Document History

Final Version	Reason for Amendment	Effective Date [dd Month yyyy]
1	First issue, public comments incorporated and published for implementation	30 October 2021
2	New template for guidelines and document number changed from 5.12 to SAHPGL-INSP-RC-01	24 June 2022
3	− Content structured in accordance with latest Guideline Template − Document title changed from Guideline for Market Surveillance of Medicines to Guideline for Post-Marketing Surveillance of Medicines and Health Products − Non-technical amendments after implementation of the guideline	27 July 2023

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Contents

Glossary

Abbreviation / Term	Meaning
Authority	means the South African Health Products Regulatory Authority established by section 2
Batch number	means distinctive combination of numbers and/or letters which uniquely identifies a batch on the labels, its batch records and corresponding certificates of analysis.
cGMP	Current Good Manufacturing Practice
Health Products (for the purpose of this guideline)	includes medical devices, *in-vitro* diagnostic medical devices (IVDs), complementary medicines, biologicals, vaccines, blood and blood products and medical gases.
INSP	Inspectorate
INN	International Non-Proprietary
IVDs	*In-vitro* Diagnostic Medical Devices
IVDs	means a medical device, whether used alone or in combination, intended by the manufacturer for the *in vitro* examination of specimens derived from the human body solely or principally to provide information for diagnostic, monitoring or compatibility purposes
Label	when used as a verb, means brand, mark or otherwise designate or describe, and when used as a noun, means any brand or mark or any written, pictorial or other descriptive matter appearing on or attached to or packed with and referring to any article or the package containing any article
MCO	Medicines Control Officer
Medicine	any substance or mixture of substances used or purporting to be suitable for use or manufactured or sold for use in— *(i)* the diagnosis, treatment, mitigation, modification or prevention of disease, abnormal physical or mental state or the symptoms thereof in humans; or (ii) restoring, correcting or modifying any somatic or psychic or organic function in humans, and includes any veterinary medicine,
OOS	Out of Specification
PI	Professional Information
PIL	Patient Information Leaflet

Abbreviation / Term	Meaning
PMS	Post-Marketing Surveillance
Post-Marketing Surveillance	Post Marketing Surveillance (PMS) refers to the practice of monitoring quality, safety and efficacy of medicines after they have been registered, authorised and released onto the market
QAS	Quality Assurance Sampling
RC	Regulatory Compliance
Risk assessment	means identifying and characterizing the nature, frequency, and severity of the risks associated with the use of a product. Risk assessment occurs throughout a product's lifecycle, from the early identification of a product as a candidate, through the pre-marketing development process, and after marketing.
SADC	Southern African Development Community
SAHPGL	SAHPRA Guideline
SAHPRA	South African Health Products Regulatory Authority
Sample	means number of units (i.e. same product name, manufacturer, dosage form, package size, packaging material and strength) representing the same batch and collected at the same location/outlet.
Sampling	means is the process of selecting units (e.g., batch, people, organizations) from a population of interest so that by studying the sample we may fairly generalize our results back to the population from which they were chosen.
SF	Substandard and/or Falsified Medicines
The Medicines Act	Medicines and Related Substances Act, 1965 (Act 101 of 1965), as amended
TMDA	Tanzania Medicines and Medical Device Authority
Vigilance	in relation to a medicine, medical device or IVD, means the continuous monitoring and evaluation of its safety, efficacy and performance profile and the management of any risk throughout its life-cycle
WHO	World Health Organisation
ZAZIBONA	Collaborative registration initiative which includes Zambia, Zimbabwe, Botswana and Namibia

1. INTRODUCTION

This document pertains to the objectives and processes for Post Marketing Surveillance (PMS) for medicines and health products conducted by the South African Health Products Regulatory Authority (SAHPRA) in collaboration with other stakeholders. The role of other stakeholders will be determined by SAHPRA. It describes the measures taken to ensure the ongoing compliance of medicines and health products with the requirements for safety, quality, and performance after they are placed on the market.

All regulatory systems recognize the importance of quality medicines and health products. There are several factors that may lead to medicines not fully complying with quality requirements and specifications. Those factors may include manufacturing processes, transportation, storage, distribution, handling and dispensing to patients.

South Africa imports numerous medicines and health products and thus imposes a risk of substandard and/ or falsified medicines and health products (SF). This may allow unsafe and ineffective medicines and health products on the market resulting from inadequate enforcement, existence of unofficial ports of entry, unscrupulous dealers, inadequate cooperation and support from other law enforcement agencies and failure of manufacturers to comply with Current Good Manufacturing Practices (cGMP) requirements. This may pose risks to public health and consequently lead to significant increase in morbidity and mortality rates. It thus necessitates the existence of a surveillance system to continuously monitor quality, safety and effectiveness of medicines and health products circulating on the market.

PMS refers to the practice of monitoring quality, safety and efficacy of medicines and health products after they have been registered and released onto the market. SAHPRA has been implementing its regulatory strategies aiming at ensuring that medicines and health products which are being circulated and used in South Africa are of good quality, safety and efficacy as well as performing adequately to protect and promote public health. SAHPRA has developed these guidelines to guide the stakeholders in the medicines and health products supply chain on how the SAHPRA PMS program for monitoring purposes will be conducted. Adherence to these guidelines may lead to effective and functional surveillance systems that will increase confidence of the public and lead to the existence of a cost-effective program.

SAHPRA conducts the PMS program through planning of sampling, sample collection, analysis and reporting.

The program review may be necessitated by changes in applicable laws and regulations governing SAHPRA when the need arises.

1.1 Purpose

The Guideline outlines requirements that should be met in PMS. This PMS guideline deals with:

- the identification and selection of medicines and health products to be monitored;
- consideration of geographical coverage;
- consideration of facilities to sample from;
- development of sampling plan;
- development of PMS protocol;
- training of sample collectors;
- sample collection;
- sample testing;
- evaluation of the label, Professional Information (PI) and Patient Information Leaflet (PIL);
- report Out of Specification (OOS) testing results and non-conformances of label, PI and PIL to Holder of the Certificate of Registration (HCR) and relevant SAHPRA unit;
- enforcement; and
- monitoring and evaluation.

1.2 Scope

Medicines include both human and veterinary medicines, and the surveillance may also include the following health products: medical devices, *in-vitro* diagnostic medical devices (IVDs), complementary medicines, biologicals, vaccines, blood and blood products and medical gases.

This guideline applies to imported or locally manufactured medicines and health products.

Coverage may also include certain public and private organizations and health facilities to include all levels in the supply chain.

2. LEGAL PROVISION

The Medicines and Related Substances Act, 1965 (Act 101 of 1965), as amended (hereinafter 'The Medicines Act') makes provision for performing PMS in terms of Section 2B(1)(d) and Section 35(1)(xiii) which states:

Section 2B Functions of Authority

(1) The Authority must, in order to achieve its objects—

d) ensure that evidence of existing and new adverse events, interactions, information with regard to post-marketing surveillance and vigilance is being monitored, analyzed and acted upon.

Section 35. Regulations

(1) The Minister may, in consultation with the Authority, make regulations—

(xiii) relating to the responsibilities of both medical device and *In-vitro* Diagnostic (IVD) establishments and users of medical devices and IVDs, in relation to the use, training, maintenance, calibration, post-marketing surveillance, sterilization, disinfection, recall, decomposition, decommissioning or decontamination of medical devices and IVDs.

3. REQUIREMENTS FOR POST-MARKETING SURVEILLANCE

3.1 Identification and selection of medicines and health products to be monitored.

Identification and selection of medicines and health products to be monitored is one of the most important steps in the preparation of the PMS program. Identification and selection shall be driven by the set objectives and public health considerations. The potential public health impact of poor-quality medicines and health products should also be a key guide for selection. In either case the program should indicate criteria used in identification and selection of medicines and health products to be monitored. During identification and selection, the following may be considered:

a) Source of information such as: experience from inspection activities, dossier assessment, laboratory analysis, vigilance activities, medicines and health products information or public health programs; pharmacists and other healthcare professionals;

i. Previous surveillance reports, published studies, scientific literatures;

ii. Consumer complaints;

iii. Supplier performance;

iv. Importation data; and

v. List of registered and unregistered medicines and health products authorized under certain conditions (e.g. donation).

b) Selection criteria may include but not limited to:

i. Medicines and health products that are used for treating diseases of economic importance;

ii. Medicines and health products for diseases of common occurrence in certain regions;

iii. Medicines and health products for priority endemic diseases;

iv. Medicines and health products for common chronic diseases or life-threatening illnesses;

v. Medicines and health products which have indicated poor quality performance;

vi. Medicines and health products which are used by a specific at-risk group i.e., pregnant women, paediatric and geriatric;

vii. Medicines and health products which are prone to resistance due to non-adherence;

viii. First line medicines and health products with complicated dosage regimen;

ix. Medicines and health products which require prolonged administration to a larger population and several of them are used in combination;

x. Medicines and health products that are candidates for counterfeiting; and

xi. Medicines and health products which are potentially dangerous, unstable, or difficult to formulate.

c) Selection of medicines and health products during protocol development.

Following identification of the medicine(s) and/ or health product(s) type as indicated in section above, a medicine and/ or health product risk evaluation may be used in identification of specific medicine(s) and/ or health product(s) to be collected in the specific PMS protocol.

3.2 Selection of areas or regions to be sampled.

A number of different geographical areas should be sampled unless the objectives expressly justify targeting

only one area. Samples should be collected in various locations, as situations in rural and suburban areas often differ. Risk-based approaches may be applied to target sampling to specific geographical areas. Depending on the surveillance objectives, the following criteria may be considered when selecting areas to be surveyed:

a) Population density;

b) Incidence or prevalence of the disease for which the target medicines or health products are indicated;

c) Degree of urbanization;

d) Income level of the population in the target area;

e) Areas with complex distribution systems;

f) Areas with outlets selling predominantly unregistered and/or unauthorized medicines and health products;

g) Regions and districts bordering other countries;

h) Regions and districts that are not frequently inspected;

i) Areas with high trends of quality problems (including major towns and centres); and

j) Areas with high prevalence of diseases related to products being monitored.

3.3 Types of sample collection sites

During the planning stage, the type of sample collection sites will be reflected in the PMS Program, an example is included below:

a) Level 1 – points of entry to the market e.g., warehouses of pharmaceuticals importers [manufacturers] and other facilities supplied directly within various programs;

b) Level 2 – pharmaceuticals wholesalers and/ or distributors;

c) Level 3 – retail pharmacies and other regulated dispensing facilities, hospitals, health centres, dispensaries clinics, polyclinics and any other health facilities;

d) Level 4 –formal retail outlets (including supermarkets) and the selling of medicines and/ or health

products outside the pharmaceutical distribution system including street vendors; and

e) Level 5 – informal outlet selling medicines and/ or health products outside the approved distribution system including street vendors.

3.4 Sampling Protocol

PMS Protocol will include a well-designed sampling plan that contains information such as name(s) of the samples to be collected; unit pack; dosage form; strength; category; number of brands (containing the identified International Non-Proprietary (INN) substance(s) to be collected; number of units per sample, sampling site information and number of batches to be collected per each brand). The following should be taken into consideration during the preparation of a sampling protocol:

a) Identification of sample collection sites (regions/ districts & level);

b) Priority products or categories of medicines and/ or health products to be sampled;

c) Only facilities that potentially have targeted medicines and/ or health products for surveillance should be included in the facilities list that will undergo risk scoring (if a medicine and/ or health product is available only in the public sector all facilities in the private sector will be excluded).

d) Samples to be taken close to the point of use of the products;

e) Samples to be taken from each of the identified facilities (different levels of supply chain);

f) Define a timeframe for sampling phase;

g) Define and approve budget;

h) The protocol should inform the type of test(s) required. This will inform the minimum quantity of sample to be collected (number of units per sample);

i) The protocol should include the testing scope of the medicines and/ or health products;

j) Appropriate arrangement with the approved laboratory which will perform testing of products should be done in the planning stage;

k) Medicines and/ or health products selection:

Sample size needed and a number of units needed;

l) Facilities for sample collection:

i. Geographical Areas risk; and

ii. Facility risk.

m) Sampling plan:

i. Randomized list of facilities for sampling and substitution list;

ii. Name of medicines and/or health products to be collected at the facility;

iii. Number of units to be collected per sample;

iv. Storage and handling requirements during sample collection;

v. Transportation to laboratories; and

vi. Sampling design.

n) Testing Plan:

i. What tests are recommended for PMS;

ii. Screening method if available;

iii. What methods for testing;

iv. Risk-based approach - and expectations; and

v. Laboratory testing and timelines.

o) Evaluation of the printed packaging material by SAHPRA Medicines Control Officer (MCO) in terms of the approved label, PI and PIL per the registration dossier as well as to the provisions of the Medicines Act and the relevant Regulations 10, 11 & 12 and Guidelines SAHPGL-CEM-02 Guideline for Professional Information for Human Medicines (Categories A and D) and SAHGL-CEM-03 Guideline for Patient Information Leaflet for Human Medicines (Categories A and D); and

p) Evaluating Results and Report Preparation.

3.5 Sample Collectors

Samples will be collected by trained SAHPRA officials.

3.6 Laboratory Testing

a) A suitably World Health Organization (WHO) prequalified, or ISO 17025 certified laboratory shall be used for all tests.

b) The specific tests to be carried out will depend on the medicines and/ or health products collected and the specific objectives of the survey.

c) An official monograph will be used whenever needed. The method described in the dossier may be used for products containing substances or combinations thereof that do not have an official monograph available.

d) Pharmacopoeia Standard according to WHO recognized and/ or validated method of analysis for new molecules shall be used.

3.7 Evaluating Results and Report Preparation

a) The results would be evaluated by experts.

b) Report shall be prepared, approved and published.

3.8 Results dissemination

a) A publication of PMS report shall be shared with the relevant stakeholders.

b) The information should be made available to the public e.g., through reports, SAHPRA website, conference and when applicable in academic journals.

c) The information may also be shared with other regulatory agencies, reliance partners, WHO and harmonization initiatives within ZAZIBONA (Collaborative registration initiative which includes Zambia, Zimbabwe, Botswana and Namibia) and Southern African Development Community (SADC).

3.9 Enforcement

a) The objective of PMS is to determine the quality of medicines and/or health products and adherence to the legally set standards. Every PMS report should contain a summary of the results and recommendations.

b) The Authority will take necessary legal actions to protect the public. Based on benefit vs risk and

proportionate to the risk, the Authority will implement appropriate action from administrative corrective action with monitoring. The enforcement will include but not limited to:

i. Close monitoring of medicines and/or health products with relevant communication, risk management and reporting in accordance with Section 2B(1)(e) of the Medicines Act;

ii. Withdrawal of medicines and/or health products in accordance with SAHPGL-INSP-RC-05 Guideline for medicine recalls/ withdrawal and rapid alerts;

iii. Recall of batches in accordance with Regulation 22(4)(i) and SAHPGL-INSP-RC-05 Guideline for medicine recalls/ withdrawal and rapid alerts;

iv. Cancellation of registration of medicines and/or health products in accordance with Section 16(1)-(4) of the Medicines Act;

v. Suspend the 22C licence of the Applicant/HCR in accordance with Section 22E(2)(a) of the Medicines Act for such period the Director-General or the Authority may determine;

vi. Revoke the 22C licence of the Applicant/HCR in accordance with Section 22E(2)(b) of the Medicines Act;

vii. Institution of disciplinary proceedings as per Law and impose penalties as set out in Section 30(1)-(4) of the Medicines Act for offences as set out in Section 29(a)-(m) of the same Act;

viii. Any other applicable legislative action(s).

3.10 Monitoring and Evaluation

Monitoring and Evaluation is important to assess program effectiveness and performance. This will be done through SAHPRA processes.

4. REFERENCES

The following related documents are referenced:

4.1 TMDA. (2019, July). Post-Market Surveillance of Medicines. Retrieved from https://www.tmda.go.tz/pages/post-marketing-surveillance-of-medicines

4.2 WHO. (2015, June). Guidelines on the conduct of surveys of the quality of medicines QAS/15.630. Retrieved from https://www.who.int/publications/m/item/qas-15.630

4.3 Medicines and Related Substances Act 101 of 1965, as amended.

4.4 Department of Health (South Africa). 2017. Medicines and Related Substances Act, 1965 (Act no. 101 of 1965): General Regulations. (Notice 859). Government Gazette, 41064:47, 25 August.

4.5 SAHPGL-CEM-02 *(Latest version)* Guideline for Professional Information for Human Medicines (Categories A and D).

4.6 SAHGL-CEM-03 *(Latest version)* Guideline for Patient Information Leaflet for Human Medicines (Categories A and D).

4.7 SAHPGL-INSP-RC-05 *(Latest version)* Guideline for medicine recalls/ withdrawal and rapid alerts.

4.8 SAHPGL-PEM—BIO-06 *(Latest version)* General Guidance Document on Quality, Safety and Efficacy requirements for Biological Medicines.

5. VALIDITY

This guideline is valid for a period of 5 years from the effective date of revision and replaces the old Guidelines for Market Surveillance of Medicines, version 2. It will be reviewed on this timeframe or as and when required.