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GUIDELINES FOR MARKET SURVEILLANCE OF MEDICINES

This document has been prepared to serve as a guidance document regarding SAHPRA Market Surveilance activities

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1. BACKGROUND

1.1. All regulatory systems recognize the importance of quality medicines. 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. During the period of development medicines are tested for short-term safety and efficacy at a limited duration to a limited number of carefully selected individuals who have been "controlled" for this purpose. Therefore, there are possible risks after medicines have been released onto the market resulting in adverse effects to the population since medicines are then used in real-life scenarios as opposed to highly controlled pre-marketing trials.

1.2. South Africa imports a number of medicines and thus imposes a risk of substandard and/or falsified medicines (SF). This may allow unsafe and ineffective medicines 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 cGMP requirements. This may pose risks to public health and consequently lead to significant increase in morbidity and mortality rates. It thus necessitated the existence of a surveillance system to continuously monitor quality, safety and effectiveness of medicines circulating on the market.

1.3. Post Marketing Surveillance (PMS) refers to the practice of monitoring quality, safety and efficacy of medicines after they have been registered and released onto the market. The South African Health Product Regulatory Authority (SAHPRA) has been implementing its regulatory strategies aiming at ensuring that medicines or medical devices which are being circulated and used in South Africa are of good quality, safety and efficacy as well as performing adequately in order to protect and promote public health. SAHPRA has developed these guidelines to guide the stakeholders in medicines supply chain on how SAHPRA PMS programme 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 programme.

1.4. The design to be used in post marketing surveillance programme will depend on the objectives of the study. This must be clearly defined together with any specific concerns to be investigated and should be identified and explicitly addressed by the proposed methods including sampling plan, sample collection and analysis. The post market surveillance programme will be reviewed every three years. However, the review may be necessitated by changes in applicable laws and regulations governing SAHPRA when the need arises. Suggestion for

amendments, additions and improvements to the programme should be directed to the CEO.

2. PURPOSE OF THE GUIDELINES

2.1. To develop a medicine information data bank on quality of medicines in circulation and disseminate such information to stakeholders involved in medicines supply chain.
2.2. To promote communication and cooperation between stakeholders and partners involved in medicines supply chain.
2.3. To identify possible causes of inferior quality of specific products to which patients are exposed.
2.4. To determine registration status of products on the market and to assess the quality and safety of medicines or medical devices on the market and conformity with acceptable specifications as declared in the registration dossiers.
2.5. To evaluate the quality of selected medicines 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 proposing appropriate actions.
2.6. To compare the quality of domestically produced and imported medicines in order to recommend appropriate regulatory actions and adjust pharmaceutical policy.
2.7. To propose possible strategies and implementation plans to address the problems identified by the survey based on usage, dissatisfaction or adverse events reported.
2.8. To test the quality of selected medicines in order to support the Authority in identification of manufacturers/importers? that are not in compliance with quality standards and regulatory measures.
2.9. To combat the spread of counterfeit/substandard medicines in South Africa.
2.10. To find out if, within a selected category of medicines, 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.

3. SCOPE

3.1. SAHPRA is charged with the responsibility of regulating medicines from clinical trial phase to post-marketing surveillance phase.
3.2. Medicines include both human and veterinary medicines, and they also include herbal medicines, biologicals, vaccines, blood and blood products and medical gases.
3.3. This guideline applies to import health products for commercial, personal, animal health, or any other purpose.
3.4. The scope includes special authorisation application process, applicable fees and the turnaround time for finalizing an application.
3.5. Coverage may also include certain public and private organizations and health facilities to include manufacturers of medicines, importers and distributors, wholesale and retail pharmacies, hospitals, health centres dispensaries and clinics.

4. DEFINITIONS AND ABREVIATIONS

"**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.

"Medicines" means human medicines, veterinary medicines which are registered and regulated by SAHPRA in accordance with Act 101 of 1965

"OTC medicine" Over The Counter medicine means medicine available to the public without a prescription

"Pharmacovigilance" is part of post marketing surveillance that involves science and activities relating to the detection, assessment, understanding and prevention of adverse events or any other medicine related problems.

"Post marketing surveillance" means clinical trial or other investigations usually conducted under a single protocol to gather specific information about an approved medicinal or biological product.

"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.

"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.

"**HPLC**" High Performance Liquid Chromatography is a process of separating components in a liquid mixture

Abbreviations:

BP	- British Pharmacopoeia
CEO	- Chief Executive Officer
cGMP	- Current Good Manufacturing Practices
CoA	- Certificate of Analysis
DBS	- Directorate of Business Support
DLS	- Directorate of Laboratory Services
EAC	- East African Community
HPLC	- High Performance Liquid Chromatography
MCO	– Medicine Control Officer
NGOs	- Non-Government Organizations
OTCs	- Over The Counter medicines
Ph Eu	r - European Pharmacopoeia
Ph.Int	- International Pharmacopoeia
PMS	- Post Marketing Surveillance
PV	– Pharmacovigilance
SADC	- Southern African Development Community
SAHPRA	- South African Health Product Regulatory Agency
SAPC	- South African Pharmacy Council
SF	- Sub-standard/ Falsified
SOP	- Standard Operating Procedure
SWOC	- Strength/ Weakness/ Opportunities/ Constrains
TLC	- Thin Layer Chromatography
USP	- United States Pharmacopoeia
WHO	- World Health Organization

5. REQUIREMENTS FOR MARKET SURVEILLANCE

5.1. Identification and selection of medicines to be monitored

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

of medicines to be monitored. During identification and selection the following should be considered:

a) **Source of information** such as: Experience from inspection activities, dossier assessment, laboratory analysis, pharmacovigilance activities, drug information or public health programmes; pharmacists and other health-care professionals;
   i. Previous surveillance reports, published studies, scientific literatures;
   ii. Customer complaints;
   iii. Supplier performance;
   iv. Importation data
   v. List of registered medicines and unregistered medicines authorized under certain conditions (e.g. donation)

b) **Set criteria which shall include but not limited to:**
   i. Medicines that are used for treating diseases of economic importance such as anti-retroviral, anti-malarial and antituberculosis;
   ii. Medicines for diseases of common occurrence in the certain regions;
   iii. Medicines for priority endemic diseases;
   iv. Medicines for common chronic diseases or life-threatening illnesses
   v. Medicines which have indicated poor quality performance;
   vi. Medicines which are used by a specific at-risk group i.e. pregnant women, paediatric and geriatric.
   vii. Medicines which are irrationally prescribed and dispensed;
   viii. Medicines which are prone to resistance due to non-adherence;
   ix. First line medicines with complicated dosage regimen;
   x. Medicines which require prolonged administration to a larger population and a number of them are used in combination;
   xi. Medicines that are candidates for possible counterfeiting; and
   xii. Medicines which are potentially dangerous, unstable or difficult to formulate.

5.2. 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. Depending on the survey objectives, the following criteria may be considered when selecting areas to be surveyed and may appear in the programme:

a) Population density;
b) Incidence or prevalence of the disease for which the target medicines 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 illegal medicine
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);
j) Areas with high prevalence of diseases related to products being monitored; and

k) Regions and districts which are highly populated.

5.3. Types of sample collection sites

During the planning stage, the type of sample collection sites by Applicants will be understood and reflected in the PMS Programme.

a) Level 1 – points of entry to the market e.g. warehouses of pharmaceuticals importers or manufacturers and other facilities supplied directly within various programmes
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 – informal outlets selling medicines outside the approved distribution system including street vendors.

5.4. Sampling Plan

PMS Programme will include a well-designed sampling plan that contains information on name(s) of the samples to be collected; unit pack; number of unit pack per batch; quantity; cost; dosage form; strength; category; sampling sites(s); number of brands to be collected; and number of batches to be collected per each brand. The following should be taken into consideration during the preparation of a sampling plan:

a) Identification of sample collection sites (regions/districts & level);
b) Include all medicinal products to be sampled;
c) Samples to be taken close to the point of use of the products;
d) Samples to be taken from each of the identified facilities (manufacturing facilities, ports of entry, distribution outlets such as importers and wholesalers, pharmacies, hospitals, health centres, dispensaries and clinics);
e) Define a timeframe for sampling phase;
f) Define and approve budget; and
g) Appropriate arrangement with any approved laboratory which will perform testing of products should be done in the planning stage.

5.5. Training of Sample Collectors (SAHPRA officials or delegate)

Documented standard procedures for training, sampling and sample handling should be available. To ensure successful implementation of PMS programme, training must be provided at all implementation levels. Training will also include:

a) Sampling planning, methodology and procedures;
b) Screening techniques to include physical inspections, disintegration testing, colour reaction and TLC interpretation;
c) Reporting of results;
d) Analysis of samples and interpretation of results; and
e) Monitoring and evaluation of the programme

5.6. Sampling design

a) Standard operating procedures must be in place

b) Samples should be collected from different batches, different locations and from all available sectors to accurately represent the selected medicines.

c) Sampling should be performed by trained sample collectors and should adhere to the approved sampling plan.

d) Sampling site can be different from one region/ district to another depending on products to be sampled.

e) Samples must be collected properly in their original containers or packages although any sample (s) which is not in its original container must also be collected as long as all information is recorded on the PMS sample collection form.

f) Sampling tools required must be provided (Sampling bags, forms, marker pen, knives, spoons etc) and resources.
Samples should be packed and stored in a manner that prevents any deterioration, contamination or adulteration

g) Samples should be stored in accordance with the manufacturers recommended storage conditions

h) Adequate measures have to be taken to ensure that samples are transported to the laboratory in good conditions and should prevent any physical damage to the samples.

5.7. Sample screening and testing

a) **Sample screening (product information review)**

i. Product information review and their package will help to give information about the manufacturing source, sample integrity and identification of counterfeit and spurious medicines.

ii. All physical samples and labels would be reviewed for conformity to appearance and labelling requirements as prescribed in regulation 10 of the Medicines and Related Substances Act, 101 of 1965.

iii. Examined against information provided in the respective samples e.g.
   a. Oral solids are checked for spots, moulds, abrasions, colour, odour, shape etc.
   b. Oral liquids are examined for container leakage, particles, homogeneity, tampering, fill volume, odour, colour etc.
   c. Labels (primary and secondary) and package inserts are examined for information, size and type of container, format, shape, print, stickiness, legibility and indelibility.

iv. Information should be entered in the Product Information Review (PIR) form - one sample per one PIR form

b) **Sample screening (simple basic tests)**

i. Simple disintegration test, colour reaction test and chromatography tests such as HPLC or TLC should be conducted as per developed service level agreements for screening and laboratory testing

ii. All samples should be subjected to screening testing

5.8. **Laboratory Testing**

a) Approved laboratory shall contract a suitable WHO prequalified laboratory for all tests.
b) All failed/doubtful and 10% of passed sample(s) should be subjected to confirmatory testing.
c) The specific tests to be carried out will depend on the products collected and the specific objectives of the survey.
d) An official monograph will be used whenever needed.
e) Pharmacopoeia Standard according to WHO recognized and/or validated method of analysis for new molecules. The following monographs shall be used unless otherwise:

i. British Pharmacopoeia (BP)
ii. European Pharmacopoeia (Ph Eur)
iii. United States Pharmacopoeia (USP)
iv. International Pharmacopoeia; and
v. Any other that may be recognized by the Authority

5.9. **EVALUATING RESULTS AND REPORT PREPARATION**

a) Results shall include information pertaining to samples collected, collection points, analytical tests and results obtained, review of approved summary of product characteristics, associated risk factors and potential reasons for failure of product's quality.
b) The results should be evaluated by experts (including risk assessors and epidemiologists).
c) Evaluation should include the statistical treatment of data, graphical presentations, trend analysis and indications of success or failure of the programme
d) Report shall be prepared in line with approved reporting format, logged in a tracker and shared with management.

5.10. **RESULTS DISSEMINATION**

a) Publication of report shall be to the relevant stake holders depending on the risk.
b) The information should be made available to the public e.g. through reports, SAHPRA website, conference and when applicable in international journals.
c) The information may also be shared with other regulatory agencies, reliance partners, WHO and harmonization initiatives within ZAZIBONA and SADC

5.11. **ENFORCEMENT**

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

b) The Authority should institute all necessary legal actions to protect the public. The enforcement will include but not limited to:

i. Withdrawal of products
ii. Recall of batches
iii. De-registration of products
iv. Prosecution of offenders
v. Institution of disciplinary proceedings as per Law
vi. Any other necessary legal action(s)

5.12. MONITORING & EVALUATION

Monitoring and Evaluation is important to assess programme effectiveness and performance. It will be conducted throughout the programme by an identified PMS Task Force using developed implementation monitoring tool.

5.13. ROLES AND RESPONSIBILITIES

a) The maintenance and enhancement of health and safety is a responsibility that is shared between government, industry, consumers, healthcare professionals and their respective associations. The key stakeholders in PMS include:

i. Patients/ Public
ii. Pharmacy practitioners and other healthcare workers
iii. Pharmaceutical Industries
iv. Programs in the Department Of Health
v. Private and Public Procurement and Distribution Agencies
vi. Development Partners
vii. Regulatory bodies
viii. Professional organizations such as SAPC, Nursing Council, etc
ix. NGOs
x. Other stakeholders and partners

b) **SAHPRA** has primary responsibility to enforce compliance

i. Core mandate is to ensure the provision of quality, safe and efficacious medicines to the public
ii. Coordinate sample collection from each site
iii. Laboratory testing
iv. Evaluation of analytical results
v. Report writing for publication and dissemination of the PMS report to all stakeholders
vi. Take action as appropriate
vii. In the case of non-conformity with specifications, SAHPRA can impose sanctions as defined in law.

c) **SAHPRA**

The coordinator will be in charge of:

i. Coordinating the PMS activities
ii. Ensure the development of a PMS Programme including sampling plan;
iii. Supervise the implementation of the Programme
iv. Ensure samples are collected as per plan

v. Ensure that samples are analysed accordingly
vi. Write and disseminate the report; and
vii. Handle any other issues that may arise during the implementation period

5.14. POST MARKETING SURVEILLANCE TASK FORCE

a) The PMS task force will be based at SAHPRA and will include experts from different representatives from units such as:
   i. Pharmacovigilance team
   ii. Quality
   iii. Inspectorate
   iv. Licensing
   v. Chief executive Officer's (CEO) Office

b) Any of the following fields of specialization, amongst others, may be invited if necessary depending on the product monitored:
   i. Medical specialists
   ii. Statistician
   iii. Public health specialist
   iv. Microbiologist
   v. Biotechnologist

c) The main functions of PMS Task force will include, but not limited to:
   i. Developing PMS programme and sampling plan
   ii. Assessment of the Programme and sampling plans before being rolled out
   iii. Oversee the implementation of PMS Programme
   iv. Monitoring and evaluation of PMS activities
   v. Release of PMS Reports to the public, Industries, programs and other stakeholders
   vi. Recommending necessary regulatory actions to the Authority

d) **CEO's office will be responsible for:**
   i. Training of staff involved in PMS activities
   ii. Ensure sampling is carried out as per proposed sampling plan
   iii. Ensure appropriate labelling, storage and transportation of samples collected directly to SAHPRA
   iv. Verify reports from SAHPRA

e) **Public Health Programs**

Provide authorization to data collection teams for gathering samples from relevant sites.

f) **Development Partners**
   i. Provide technical and financial assistance in the implementation of PMS activities
   ii. Participate in the discussion and dissemination of results

iii. Ensure follow-up, monitoring, evaluation, and execution of PMS activities as per the budget
iv. Provide training as needed

g) **Procurement Agencies**
   i. Provide samples available to sampling team
   ii. Provide samples to health facilities to replenish withdrawn samples if necessary
   iii. Participate in discussion on findings and implementation of regulatory action as directed by SAHPRA

5.15. STRUCTURE OF POST-MARKET

Post Marketing Surveillance programme shall contain the following details:

a) **Introduction**

Provide any background information on the issue of quality, safety and effectiveness of medicinal product and justification of conducting PMS for the specific products.

b) **Definition of terms**

Provide meaning of terms used in the document (If any)

c) **Situation analysis (SWOC analysis)**

This is a systematic collection and evaluation of organization internal and external environment that may influence organization performance and choice of strategies. During the documentation of situation analysis, SAHPRA should consider the following:-

   i. Needs of PMS programme
   ii. Current and future strengths, weaknesses, opportunities and constrains.

d) **Risk Assessment**

Risk Assessment is an effective means of identifying process risks and determining the most cost effective means to reduce those risks. Risks must be identified correctly before SAHPRA can develop PMS Programme. SAHPRA should use both quantitative risk assessment and qualitative risk assessment tools and methods depending on availability of data, and information systems to support the assessments.

e) **Criteria for Selection of Medicines**

In preparing PMS programme the selection of medicines is among the critical factors. The criteria for selection of products to be surveyed should be considered as explained in section 2.5.1 of these guidelines.

f) **Objectives of the PMS Programme**

Explain the broad objective and specific objectives of the proposed PMS Programme.

g) **Methodology**

This section explains what activities to be done in implementing PMS programme. These may include preparation of sampling plan, selection of sampling areas, training of staff involved in activities, sampling screening, laboratory testing, evaluation of results and report preparation.

h) **Enforcement**

This section explains the necessary legal actions which will be instituted in order to protect public from further harm and to improve quality of the products on the market.

i) **Organization, Management and responsibilities**

The implementation of PMS should involve all necessary stakeholders inside and outside the Authority. This section explains how the programme will be organized, managed and what are the key responsibilities of each stakeholder participating in the programme.

j) **Resource needed**

This section mention all resources needed in implementing PMS programme. Detailed Budget of PMS activities should be prepared and attached.

k) **Monitoring and evaluation**

This section explains how the implementation of PMS programme should be monitored and evaluated.

l) **Results and Dissemination**

PMS report should be made available to the public through different ways of communication. This section explains how the information will be communicated to the public and all other stakeholders.

m) **Forms**

The following are the key documents which should be attached in the proposed PMS programme but not limited to:

i. Timeline of the Programme
ii. Sampling plan
iii. Sample collection form
iv. Product information review and screening form
v. Test request Form
vi. PMS Process Flow Chart
vii. Budget of PMS programme
viii. PMS reporting format
ix. Tracker

5.16. Key Cost Elements

The cost elements for a post marketing surveillance activity include but not limited to:

a) Administrative Costs (SAHPRA)
b) Programme development
c) Training of sample collectors
d) Travel Costs – for field work
e) Purchase of samples
f) Transportation of samples for Laboratory testing
g) Laboratory analysis
h) Evaluation of results and report writing
i) Regulatory action

6. UPDATE HISTORY

Date	Reason for update	Version & Publication
23 September 2021	First publication	Version 1, 23 September 2021