South African Health Products
Regulatory Authority
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GUIDELINES FOR MARKET SURVEILLANCE OF MEDICINES

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To develop a medicine information data bank on quality of medicines in circulation and disseminate such information to stakeholders involved in medicines supply chain.
To promote communication and cooperation between stakeholders and partners involved in medicines supply chain.
To identify possible causes of inferior quality of specific products to which patients are exposed.
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.
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.
To compare the quality of domestically produced and imported medicines 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 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 in South Africa.
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.

Document History

Version	Date	Reason for amendment
Version 1	30 October 2022	N/A
Version 2	June 2022	New Template for guidelines Change from number 5.12 to SAHPGL-INSP-RC-01

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Contents

List of abbreviations and definitions

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

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	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

1. Introduction

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. Scope

2.1. SAHPRA is authorised with the responsibility of regulating medicines from clinical trial phase to post-marketing surveillance phase.

2.2. Medicines include both human and veterinary medicines, and they also include herbal medicines, biologicals, vaccines, blood and blood products and medical gases.

2.3. This guideline applies to imported or locally manufactured health products.

2.4. 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.

3. Purpose

The Guideline outline requirements that should be meet in market surveillance. This market surveillance deal with the identification and selection medicines to be monitored. The sampling should also take into consideration the geographical area. The development of sample plan, training of sample collectors, monitoring, sample testing are some keys requirements that are addressed.

4. Background

Post-market surveillance is a set of activities conducted by manufacturers, to collect and evaluate experience gained from medicine that have been placed on the market, and to identify the need to take any action. Post-market surveillance is a crucial tool to ensure that medicine continue to be safe and well-performing and to ensure actions are undertaken if the risk of continued use of the medicine outweighs the benefit. The evaluation of post-market surveillance experiences can also highlight opportunities to improve the medical product.

This document pertains to the objectives and processes for post-market surveillance for medicine conducted by manufacturers with the assistance of their economic operators, as well as market surveillance conducted by regulators, and the role of other stakeholders in these processes. It describes the measures taken to ensure the ongoing compliance of medicine product with the requirements for safety, quality, and performance after they are placed on the market.

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 Post-Market Surveillance (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. Consumer complaints;
   iii. Supplier performance;
   iv. Importation data; and
   v. List of registered medicines and unregistered medicines authorized under certain conditions (e.g. donation).

b) Set criteria may include but not limited to:
   i. Medicines that are used for treating diseases of economic importance
   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 programme's 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 will be 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 such as name(s) of the samples to be collected; unit pack; dosage form; strength; category; 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) Priority products or categories of 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 the 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) The product and the product information will help to provide information about the manufacturing source, sample integrity and identification of substandard and/or falsified medicines.

b) All physical samples and labels would be reviewed for conformity to appearance and labelling requirements as prescribed in Regulation 10, 11 and 12 of the Medicines and Related Substances Act, 101 of 1965, as amended.

c) Samples shall be examined as per the following criteria:

i. Oral Solids Are Checked For Spots, Moulds, Abrasions, Colour, Odour, Shape Etc.

ii. Oral Liquids Are Examined For Container Leakage, Particles, Homogeneity, Tampering, Fill Volume, Odour, Colour Etc.

iii. Labels (Primary And Secondary) And Package Inserts Are Examined For Information, Size And Type Of Container, Format, Shape, Print, Stickiness, Legibility And Indelibility.

iv. Simple disintegration test, colour reaction test and chromatography tests such as HPLC or TLC should be conducted

v. All Samples should be subjected to testing

5.8. Laboratory Testing

d) A suitable WHO prequalified laboratory shall be used for all tests.

e) All failed/doubtful and 10% of passed sample(s) should be subjected to confirmatory testing.

f) The specific tests to be carried out will depend on the products collected and the specific objectives of the survey.

g) An official monograph will be used whenever needed.

h) Pharmacopoeia Standard according to WHO recognized and/or validated method of analysis for new molecules shall be used. The following monographs shall be used unless otherwise:

vi. British Pharmacopoeia (BP);

vii. European Pharmacopoeia (Ph Eur);

viii. United States Pharmacopoeia (USP);

ix. International Pharmacopoeia; and

x. 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) A publication of PMS 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 academic 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; and

vi. Any other necessary legal action(s).

5.12. Monitoring & Evaluation

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

References

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

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