Medicines Control Authority of Zimbabwe

MCAZ/LED/GL-11

GUIDELINE FOR POST MARKETING SURVEILLANCE

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Table of Contents

1.0 APPLICATION

These guidelines apply to all personnel involved in Post Marketing Surveillance (PMS) activities and relevant partners involved in the sharing of resources including testing capacities, experiences and information that can enhance the effectiveness of the PMS program. These include but are not limited to stakeholders, international organizations, procurement agencies, NGOs or academic and research groups. The PMS plan is designed to cover a wide range of medicines and regulated products marketed in Zimbabwe in order to strengthen and improve their quality and safety. Ensuring that there is adequate funding is vital during the PMS planning. In a situation where resources are limited, the PMS program shall focus on medicines and parameters that pose higher risk to patients by applying risk based analysis during the planning phase.

2.0 PURPOSE

The purpose of this guidelines is to strengthen the Authority`s system for effective Post Marketing Surveillance of medicines, and regulated products including medical devices to ensure that only quality and safe medicines and other regulated products are distributed throughout the country. Effective implementation of PMS Guidelines will enable the Authority to generate scientific evidence on the quality and safety of medicines and medical devices for improved health outcome. It is important that Zimbabwe sustains a high quality and scientifically credible safety and efficacy data on these vital health commodities to enhance evidence based decision making that impacts public health.

3.0 BACKGROUND / INTRODUCTION

Post Marketing Surveillance (PMS) is a regulatory function carried out by National Medicines Regulatory Authorities in a country. It involves assessing products quality and safety to generate reliable scientific evidence required to take regulatory action to protect public health. It continuously monitors the efficacy, quality and safety of marketed products throughout their shelf life and at all levels of the supply chain. The dependency of regulatory systems on adverse event reporting alone may not capture all risks related to medicines and the use of medical devices.

The quality of medicines is its level of suitability for intended use by the end user. It also means its ability to maintain its quality throughout the distribution chain. The quality characteristics of any medicine are its safety, potency efficacy, stability and compliance with regulatory requirements such as labeling and product information leaflet. The national quality assurance policy is available to ensure the maintenance of quality from manufacturer to the end user. To ensure that quality of medicines is maintained/monitored while being distributed, USP/PQM sponsored a workshop to provide a platform for MCAZ and relevant stakeholders to discuss and emphasized the need for best practices in post marketing surveillance of Pharmaceutical products.

The regulatory activities of MCAZ that ensures the quality of medicines in Zimbabwe include:

i. Authorization/registration/licensing of medicines for marketing based on the assessment of safety, efficacy and quality.
ii. Inspection of manufacturers of the medicines for compliance with the principles of Good Manufacturing Practices (GMP); and approval of products' information.
iii. Inspection of premises for the storage and distribution of medicines.

iv. Post-marketing surveillance/pharmacovigilance.
v. Regular inspections of manufacturers, wholesalers/distributors/retailers and quality control/ testing laboratories;
vi. The analysis of samples of medicinal products.
vii. Regulation of advertising and promotion.
viii. Provision of independent information to healthcare providers, patients and the public.
ix. The quarantine, recall, and destruction of substandard and falsified medical products.
x. Enforcement of National medicine legislation.

4.0 DEFINITIONS

4.1 Post Marketing Surveillance (PMS): is a regulatory function of National Medicines Regulatory Authorities involving the assessment of safety and quality of pharmaceutical products throughout their shelf life and at all levels of the supply chain. PMS is meant to continuously monitor the quality, safety and efficacy of pharmaceutical products on the market at all levels of the supply chain.

4.2 Quality Control Laboratory: is a laboratory providing testing services that generates analytical data within a quality system framework to provide clients with an accurate and representative portrayal of a sample's constituents, enabling them to meet their regulatory and monitoring commitments. This includes medical diagnostic laboratories.

4.3 Sample: means a pharmaceutical product, medicine, or medical device in given presentation (identified by its name, content of active pharmaceutical ingredient/s (API), dosage form, strength, batch number and manufacturer) collected at the specific location. It means that the same product characterized by the same name, content of APIs, dosage form, strength, and batch from the same manufacturer collected in two different sites represents two samples. Each sample must consist of the number of dosage units (e.g. tablets, capsules, ampoules, vials, bottles) required by the sampling plan.

4.4 Overt Sample: means an obvious/ unconcealed pharmaceutical product, medicine, or device collected at a clear and open location.

4.5 Medicines: means any substance or mixture of substances which is used, or is manufactured, sold or represented as suitable for use, in:

4.5.1 the diagnosis, treatment, mitigation or prevention of disease or any abnormal physical or mental state or the symptoms thereof in man or in animals; or restoring, correcting or modifying any physical, mental or organic function in man or in animals;

4.6 Medicine or Pharmaceutical outlet: A medicine or pharmaceutical outlet means any point (licensed or unlicensed) of sale or a place where medicines are provided to individuals or other medicine providers.

4.7 Sampling plan: A sampling plan contains detailed identification of sites where samples will be collected, medicines to be sampled, minimum number of dosage units to be collected per sample, number of samples to be collected per medicine,

and total number of samples to be collected in the area for which the sampling plan is prepared. It contains also detailed instructions for sample collectors

4.7 **Storage:** means the stowing of pharmaceutical products up to the point of use.

4.8 **Storage temperature:** The temperature range stated on the product label for proper storage.

4.9 **Transportation:** is the process of moving samples of pharmaceutical products between two locations without storing them

4.10 **Validation:** Documented testing performed under controlled conditions, demonstrating that processes, methods and systems consistently produce results meeting predetermined acceptance criteria.

5.0 GUIDELINES

5.1 Post Marketing Surveillance of Pharmaceutical products

Post marketing surveillance of Pharmaceutical products provide an important source of information on the quality of Pharmaceutical product available in the market. The surveillance program must be organized in such a way that will involve stakeholders, international organizations, procurement agencies, NGOs or academic and research groups. The PMS program must be able to respond to health priorities and challenges. It is impossible to test the quality of all registered products in the country hence the need to prioritize Pharmaceutical products based on the perceived risk to the consumer. The information obtained from PMS activities is vital to enhance and maintain the quality assurance system in Zimbabwe.

Data collection on the quality of medicines, if properly executed, interpreted and used are vital for the planning of effective interventions that will improve the quality of medicines. The accuracy, reliability and interpretation of the data obtained will also depend on the PMS plan, method of sample collection and available resources among others. Post marketing surveillance study on the quality of medicines is costly, and available resources may restrict the number of samples to be collected, tested parameters, techniques to be used for analysis, or number of staff available to conduct analysis of the sample.

Steps in PMS planning.

The steps in PMS planning include the following:

Step1: Preparation of PMS protocol
Step 2: Preparation of sampling plan
Step 3: Training of sample collectors
Step 4: Procurement of samples
Step 5: Dispatch of samples (to the laboratory)
Step 6: Analytical screening of samples
Step 7: Identification of samples for full analysis
Step 8: Collation and evaluation of result for analysis
Step 9: Evaluating results
Step 10: Preparation of Draft report of survey
Step 11: Presentation of the draft report to relevant stakeholders
Step 12: Preparation of final report

Step 13: Dissemination and Publication of report

In order to sustain regular PMS activities in Zimbabwe, the MCAZ would require to establish a suitable and practical organizational structure that ensure execution of effective surveillance activities all year round. Steps 2 to 13 will be necessary for the continuous execution of PMS program.

5.1.1 Objective

i. General Objective

The objective of this guidelines is to outline the steps to consider when preparing and conducting surveillance on the quality of pharmaceutical products and other regulated products in Zimbabwe. A surveillance is expected to be carried out on regular basis, depending on the risk evaluation, resources, capacity and concluded with a meeting involving partners and stakeholders to disclose and discuss the outcome/results.

ii. Specific Objective

To provide scientific evidence on the quality and safety of medicines and other regulated products to enhance evidence based regulatory decision to improve health outcomes.

5.1.2 Main Frame

The first of this approach is recognizing the working structure for executing a successful PMS program in Zimbabwe. The PMS activity of MCAZ is tailored towards an acceptable descriptive structural organogram for surveillance activities.

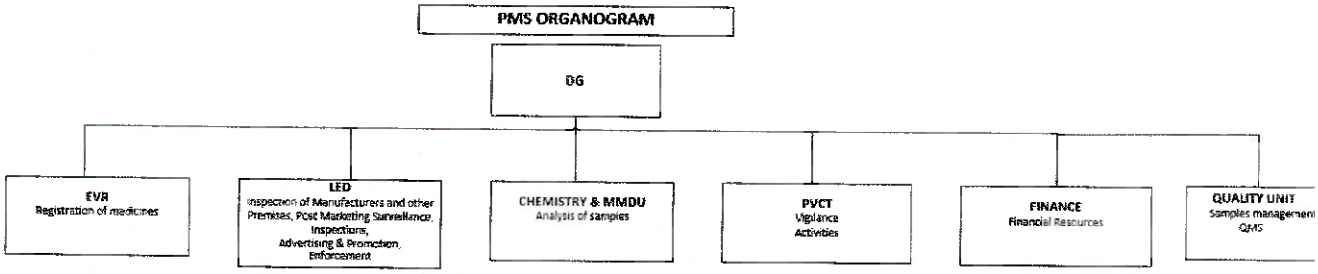
5.1.3 Management of PMS process

The management team should be responsible for coordinating and managing the PMS activities, especially quality monitoring studies by way of quality management system. MCAZ should approve PMS study plan before it commences. Responsibilities and tasks of persons having key roles in the PMS study (e.g. survey coordinator, team leader in individual areas) should be clearly outlined. There should be a clear communication link between the different departments on the PMS Activities

5.1.4 Execution of PMS Process:

Before the initiation of the program, the personnel heading the different aspect of the PMS activity shall meet and gain clear understanding of the responsibilities of the various steps from 2 to 13 such as sampling, product selection and handling, site selection, data collection and interpretation, data storage, and more.

5.1.5 MCAZ PMS Organogram



5.1.6 Training of personnel on requirements of PMS

iii. All personnel involved in inspections and sampling should be trained on the requirements of PMS. They should have the appropriate experience and competence prior to commencing their tasks. Training should be based on written standard operating procedures (SOPs).

iv. Personnel should receive initial and continuing training relevant to their role, based on written procedures and in accordance with a written training program. The responsible person should also maintain their competence in PMS through regular training.

v. In addition, training should include aspects of product security, as well as aspects of product identification, the detection of counterfeits and the avoidance of counterfeits.

vi. Personnel dealing with any products which require more stringent handling conditions should receive specific training. Examples of such products include hazardous products, radioactive materials, products presenting special risks of abuse (including narcotics and psychotropic substances), as well as time and temperature-sensitive products.

vii. A record of all training should be kept, and the effectiveness of training should be assessed and documented

5.1.7 Performing a surveillance study

Prior to the initiation of a PMS study, the objective of the study must be clearly stated and the purposes must be detailed. The PMS study should address specific public health priority, quality assurance issues, and product quality issues. In the case of product quality, the target should include selected medicines available in the market in certain areas or regions at various levels of the distribution and supply chain. The study should recommend appropriate regulatory actions that address public health concern. Due to cost implications and need for proper funding, it is recommended that the planning should be developed and executed in collaboration with key stakeholders, such as, Public Health

programs, health facilities, donors, and development partners. There shall be a stakeholders meeting to discuss the results from the PMS study and proffer recommendations and follow up actions.

Areas to be considered during the planning stage of PMS study includes the following:

i. The quality of target pharmaceutical product
ii. The information may be sought in scientific literature, alerts on medicines quality, and published studies through searches, e.g. in PubMed. It is important to gather information from inspectors, assessors, laboratory and pharmacovigilance experts and design the study with the collaboration of a multidisciplinary team mentioned above.
iii. The distribution and supply system of the target medicines
iv. In order to design the study properly it is important to understand how the target medicines are supplied in the surveillance area and how they reach patients. Knowledge of the distribution and supply chain of the target medicines enables risk-based selection of sampling sites best serving the study objectives. Complex supply chains pose higher risk of quality deterioration and should be prioritized in market surveillance activities. Information on distribution or supply chains should be available to MCAZ, Ministry of Health, National Pharmaceutical Company and other related governmental organizations.
v. Health-seeking behavior for the target medicines
vi. For some studies, it may be important to understand where different categories of patients tend to buy their medicines and what kind of product they buy. In many countries the medicines market is heavily segmented with different markets for people of different spending power. For example, the wealthier people may go to pharmacies or private clinics, whilst the poorest go to street peddlers, and people of middle income may go to private and public hospitals/clinics. There will also be brands of the same product at different prices aimed at different market segments. If such information is needed, an initial pre-surveillance study should be performed.
vii. Patients' exposure to the target pharmaceutical products
viii. Medicines with high consumption volumes should be prioritized in market surveillance activities. It may be difficult to obtain exact consumption volumes in Zimbabwe but some estimates based on distribution volumes or information from various disease control programs can be used.
ix. Brands of the target pharmaceutical products available in the surveillance, identified areas or selected outlets.
x. If the objectives of the surveillance study require a wide picture of the quality of medicines available in the market, samples of medicines produced by as many manufacturers as possible should be collected. It is normally very difficult to know in advance how many brands of a specific medicine (containing the same API in the same dosage form) are sold on the market and what their market share is. A pilot study asking for a product list at the selling points may help to collect the data needed to better plan the study.

xi. For correct understanding of all parties involved in the surveillance and proper interpretation of its results, any limitations during the study should be stated and explained.

Other aspects to include in the study are:

i. The variables and end points that will be used to answer the surveillance questions e.g. Quality Parameters, etc
ii. The surveillance approach or methodology to be used
iii. Sample size and units of observation
iv. Source of data i.e. levels of data collection at various facilities etc.
v. The data collection plan and tools
vi. Time line estimation of surveillance, what is the expected duration of the study
vii. All data analyses and statistical tests planned
viii. The content and timing of reports
ix. Dissemination of the report
x. Publication of reports
xi. Actions to be taken

5.1.8 Protocol for surveillance

Protocol for surveillance is a written detailed document that clearly outlines/describes how the surveillance should be carried out. In principle, the protocol should, contain information such as background and explanation of the study, study objectives and limitations and testing parameters.

5.1.9 Methodology

Sampling is the most critical part in a PMS activity as it determines the effectiveness of the study results. Biased sampling is a major cause of ineffective PMS study and may lead to inaccurate results and wrong recommendations. PMS results provide feedback on the effectiveness of the QA system and may influence national policies as well as a direct impact on individuals and public health. Therefore, suitably developed methodology as well as efficient training of personnel involved in the PMS activity is paramount. All SOPs, and instructions necessary to execute the study should be made available to all personnel, and there should be evidence of clear understanding of these materials and processes and procedures. It is recommended that sound statistical approaches be used in sampling to make the sampling scientific and representative of the entire population of study.
Previous studies, if any, should be used as means to gather more information relevant to the study. Some examples of questions to be asked may include but not limited to:

i. What percentage of sampled medicines failed quality testing?
ii. What quantity of sampled medicines failed quality testing at different levels of the regulated distribution chain and in the informal market?
iii. What quantity/percentage of medicines sampled at different geographical regions failed quality testing?
iv. What quantity/percentage of samples of medicines produced in Zimbabwe and samples of imported medicines failed quality testing?

v. Which specific quality test does the selected medicines fail?
vi. Are any of the deficiencies critical, i.e. could they substantially affect treatment efficacy and/or cause harm to patients?
vii. What is the registration status of sampled medicines and what percentage of registered and unregistered medicines failed quality testing?
viii. What are the supply chains by which poor-quality medicines are distributed and what market segments do they share?
ix. Are there any indicators of poor storage and distribution conditions which influence quality of sampled medicines?
x. Are there poor-quality medicines in the selected area, border checkpoint, etc.?
xi. What is the proportion of poor-quality medicines being sold?
xii. Does the proportion of poor-quality medicines exceed a predetermined level (if any)?
xiii. Has the quality changed for a medicine, or medicine category, or in an area (in case of repeated random surveys with consistent design)?
xiv. What action was taken from the previous observations or outcome?
xv. What was the impact of the observation or outcome on patients or population health?
xvi. Was there a systematic evaluation of the previous issues, and how was it resolved?
xvii. Is there a reporting mechanism to inform WHO, manufacturer or safety alert notice?

5.1.10 Selection of sites for PMS study

Different geographical areas should be selected for PMS study unless the objectives explicitly justify targeting a specific area. Samples should not be collected only in the capital city, as situations in rural and suburban areas are often very different. Depending on the study objectives, the following variables may be considered for selection of sites for PMS study.

i. Population density
ii. Incidence/prevalence of the disease for which the target medicines are indicated
iii. Level of risk of poor-quality medicines, e.g. higher risk can be at trade routes across country borders, areas where poor-quality medicines have been previously found, areas where formal health services are limited, areas where MCAZ has little or no resources to monitor the distribution of medicines;
iv. Number of surrounding villages;
v. Income level of the population in the target area; and
vi. Areas with complex distribution systems.

5.1.11 Selection of Pharmaceutical Products for PMS study

A risk based approach may be deployed to establish the rationale for the selection of medicines which may include:

i. Probability of occurrence of a quality problem, e.g. complexity of manufacturing process, stability etc.
ii. Exposure of patients to the medicine and seriousness of potential health hazards amongst others. The selection criteria could include epidemiology, geographical, accessibility, QA issues, product specification, public health, enforcements, consumer complaints and herbal products.

The category of pharmaceutical products to be studied may be characterized to include the Content of APIs, Therapeutic group classification, Formulation, Specific program under which they are supplied, and the manufacturer or distributor declared on the label.

If collection of commonly used products is required, a pre-study investigation of treatment-seeking behavior may be necessary

Working together with other sectors, such as, public health programs, the Ministry of Health and Child Care, Health care program centers, and pharmacies may help to identify products used commonly.

5.1.12 Selection of sample collection sites

In Zimbabwe, there are various types of pharmaceutical outlets and these are classified as:

i. Government health facilities
ii. Central Medical Store(s) (Natpharm) from the different provinces
iii. Selected Health Facilities in urban and rural areas in the country such as primary, secondary, and tertiary institutions
iv. Private health facilities
v. Manufacturers
vi. Wholesale centers
vii. Private Hospitals/ Clinics
viii. Pharmacies
ix. Non-governmental Organizations (NGOs)

The other type of classification for sample collection sites are based on the level of activity in the supply chain:

Level 1- Points of entry to the market, e.g. warehouses of importers or manufacturers, central medical stores, NGO central stores, procurement centers or other facilities supplied directly within various programs, central wholesalers/distributors;

Level 2- Pharmacies and other regulated retailers, dispensing facilities, hospitals, health centers, sub-health centers, district hospitals, clinics, treatment centers, health posts, community health workers;

Level 3- Informal outlets selling medicines outside the approved distribution system, e.g. kiosks, street vendors, grocery shops

Sample collection should be performed in both the public and private sectors as well as in the "informal market" which includes unlicensed outlets. Types of sites for sample

collection should be selected in a way to best serve the study objectives and the selection should be explained.

Quality of samples collected in the supply chain close to the point of sale to patients (Levels 2 and 3) may be influenced by distribution and storage conditions. If the medicines qualities are compromised due to degradation from distribution and storage problems, collection of additional samples of the same product at level 1 may highlight the bridge in the quality assurance system of supply chain management.

Samples collected at points of entry to the market (Level 1) may be less affected by storage and distribution conditions they may encounter during in-country distribution. Sampling at this point in the supply chain has the advantage of identifying the quality of products as supplied by manufacturers and detecting quality issues before the products reach patients. Corrective actions may be more easily put in place if the results are quickly available.

Once the types of sample collection sites are selected, the areas/states/zones to be sampled need to be mapped. The sites where samples will be actually collected in the study should be identified according to address and type of facility. Good local knowledge of the distribution and supply chain is required. MCAZ should develop a list of the outlets where itinerant vendors or sellers buy their medicines.

Sentinel site monitoring

Sentinel site monitoring involves following the quality of medicines in a particular locality through time. There are no common rules as to whether these sites should be chosen on the basis of potentially important variables such as rural versus urban and private versus public outlets, or as to sampling design (i.e. convenience or random samples). The power of this methodology resides in allowing longitudinal changes to be followed in one place but data from fixed sentinel site monitoring should be interpreted with caution. Sentinel site monitoring suffers from the disadvantage that shop owners may soon realize that they are being sampled, change their behavior accordingly and thus are no longer representative.

Types of Sampling

Various sampling methods can be used for of sample collection at study sites. The choice depends on the objectives of the study, the risks and consequences associated with inherent decision errors and biases and available resources. Some key points to remember during sampling as well as some sampling techniques are highlighted below.

i. Samples are to be procured taken close to the point of use of the products
ii. Samples are procured from importers, wholesalers, hospitals, clinics, and pharmacies as designed for the program.
iii. Healthcare staff at sampling sites should be informed of sampling program and the reasons to enhance their cooperation.
iv. Sample collector, form should be completed at the time of sampling should be witnessed by personnel on sites. Information on sample collection form includes details of product name, product strength, pack size, batch number, expiry date, site of sampling, and storage conditions at sampling sites.
v. SOP should be in place to ensure sampling of selected medicines

Convenience sampling

Convenience sampling is a non-probability sampling technique based on the judgment of the PMS study planner. The sites, however, should not be identified just because of their convenient accessibility and proximity. There should be defined rules guiding the selection to best reflect the study objectives. Whenever convenience sampling is used, it should be reported how the sites were identified and which types and proportion of the pharmaceutical outlets the selection represents.

Convenience samplings are simple and do not necessarily need complete lists of outlets in defined areas which may be difficult to obtain. However, they are inherently prone to biases which have to be considered when interpreting the survey outcomes. It is a technique predominantly used for selection of sample collection sites by, e.g. Medicine regulatory authorities. To utilize resources in a most efficient way MCAZ should focus on outlets where the risk of poor-quality medicines occurrence is high. When selecting sites, the risk analysis should consider, e.g. the way of medicines distribution to the site, transport conditions, storage conditions and handling of products in the site, experience of MCAZ with the distribution chain and sites.

The results of convenience sampling cannot be generalized to other areas, even within the same country, or reliably interpreted over time. However, convenience samplings may provide the evidence to support regulatory actions or signal of a quality problem. If convenience sampling does indicate that a medicine has quality problem, further investigation or regulatory actions can be initiated. If a wider picture is needed, subsequent studies with probability sampling can be designed. If convenience sampling does not demonstrate a problem, one should bear in mind that this may be a false negative result. It is important to explain the limitations of this technique in reports and scientific papers.

Random sampling

Random sampling is a probability sampling technique that, with sufficient sample size, will give reliable estimates (with confidence intervals) of the prevalence of outlets selling poor quality medicines. Formulas for calculation of a sample size for random sampling can be found in the relevant literature. The disadvantages of random sampling are the large sample sizes needed, necessity of complete lists of the locations of the target outlets and the additional costs in labor and time. In addition, it is important to recognize that a random sampling will only produce reliable and useful information if the list of outlets and actual within-outlet sampling is in concordance with the primary aims of the study. For example, a random sampling of the quality of medicine in the private sector when most patients obtain this medicine in the public sector would not be useful, nor would a random sampling using overt shoppers for a medicine which the outlet staff know should not be sold to patients. Comparisons with subsequent estimates using the same sampling method should be valid and will allow the evaluation of interventions.

Stratified Sampling

Stratified sampling is a probability sampling technique wherein the researcher divides the entire group of investigated subjects (e.g. outlets) into different subgroups (layers/strata), then randomly selects the final subjects proportionally from the different subgroups. Stratified sampling can be used to adjust for potential differences, e.g. sales volume, type of customers or geographical, trade and socioeconomic variables (such as rural versus

urban, private versus public areas and one geographic area versus another) may be considered. Stratification requires adjustment of the sample size calculation. Sampling proportional to number of outlets will be more efficient compared to simple random sampling. It is important that the randomization procedure uses formal random number tables or statistical software.

Sampling plans

Sampling plans should be prepared for each area/province involved in the survey and should be in compliance with requirements of the study protocol and must include:

i. Individual sites where sample collectors should collect samples (by facility type and address, possibly including global positioning system (GPS) coordinates)
ii. Medicines to be sampled (by APIs, dosage form, strength, and, if needed, also package size)
iii. Minimum number of dosage units to be collected per sample
iv. Number of samples to be collected per medicine
v. Total number of samples to be collected in the relevant area/zones
vi. All products that are to be sampled and rationale for selecting the products
vii. Timeframe for sampling
viii. Defined, determined, and approved budget
ix. Include and inform laboratories involved for planning purposes
x. SOPs to address sampling plans
xi. Detailed instructions for sample collectors.

Number of dosage units to be collected:

The number of dosage units that should be collected per sample depends on the study objectives, medicines selected for surveillance, tests to be conducted, testing methods to be employed and available resources. To protect integrity of samples and avoid quality deterioration before testing, dosage units should not be taken out of the original primary and secondary packaging. Only intact and unopened packages should be collected. Sampling plans normally define the minimum number of dosage units to be collected per sample. In relation to the available package size and the appropriate number of packages is collected.

In PMS studies aiming to provide evidence to support regulatory actions, pharmacopeial tests performed in compliance with pharmacopeial procedures are commonly used. In such studies the principles of good practices for pharmaceutical quality control laboratories should be followed and the number of dosage units per sample should allow:

i. Conducting the planned tests;
ii. Investigation and confirmatory testing for those found to be out-of-specification (OOS);
iii. Retention samples to be used in case of dispute.

To fulfill these requirements, sufficient numbers of dosage units per sample should be collected as stated in the study protocol, which may be difficult to obtain in some outlets. It may also suggest to the outlet owner that the buyer is not an ordinary shopper in cases

when the study objectives request a mystery- shopper approach. The minimum number of dosage units to be collected per each selected medicine should be agreed with the testing laboratory. The advantage of surveillance studies using pharmacopeial/ compendial procedures is the ability to apply quality acceptance criteria as defined in pharmacopoeias. The disadvantage is rather time- and resource-demanding laboratory testing leading to lower numbers of samples which can be included in the study.

Other types of studies are quality screening surveillance studies using basic, simple tests, non-destructive techniques (such as Raman and infrared (IR) spectroscopy) or unofficial testing methods (non-pharmacopeial) to assess the identity of the API and estimate its content. Such studies cannot be used as a basis for regulatory actions but may precipitate further investigations with appropriate protocols. The advantage is that only a few dosage units can be collected per sample, a higher number of samples can be collected and the mystery-shopper approach can be used, if needed. The disadvantage is that when testing only a few individual dosage units, usual Pharmacopeial quality acceptance criteria are difficult to apply, e.g. when estimating the content of the API by testing a few individual tablets only, Pharmacopeial criteria for the assay cannot be used.

Sampling procedures ensuring that representative samples are taken by authorities, procurement agencies, manufacturers or consumers for acceptance of consignments, batch release testing, in-process controls, special controls, inspection for consumer clearance/ deterioration/adulteration or for obtaining a retention sample are described in the WHO Guidelines for sampling of pharmaceutical products and related materials. (TRS No. 929, 2005)

Sample collection

The team leader will arrange for training of sample collectors to be familiar with the project, study protocol, sampling plan and instructions for collection of samples. Staff from MCAZ, MOHCC, Natpharm and the different public health programs may provide a useful insight into the surveillance study planning.

Data collection instructions and procedures should be well understood by the sample collectors. The following principles should be included in detailed instructions for sample collectors:

i. Sample collectors should understand the written training procedures and should adhere to them.

ii. The minimum number of dosage units per sample and number of batches to be collected from each collection site for each selected medicine as indicated in the sampling plan should be adhered to;

iii. The target medicines, their dosage forms, strengths, package sizes should be defined, as outlets may have more than one brand of a particular medicine available, instructions should be provided on how to decide if a selection has to be made. It should be taken into consideration that mystery shoppers requesting a very specific brand or product may alert sellers. However, such an approach may be required if evidence suggests that only one brand of an essential medicine is afflicted by falsification or substandard production. It may be useful to consider using a specific written prescription for a number of items including the target medicine. This can reduce raising suspicion of a verbal request. Using the written prescription

format may also enable studying the quality of dispensing, labelling directions and counseling;

iv. All units of one sample must be of the same batch number;

v. The medicine samples should not be taken out of the original primary and secondary packaging (though removal from large size secondary packs is appropriate).Containers such as bottles and vials should not be opened. In cases where medicines are sold without package leaflets, or in unlabeled plastic bags coming from large sized boxes (locally repacked), or as individual dosage forms, this should be recorded;

vi. Ideally, samples collected should have at least six months remaining to expiry to allow sufficient time for chemical analysis except for products with not more than six months shelf life. However, the frequency of expired medicines is also an important outcome measure and any expired medicine found in the outlet should be recorded;

vii. The medicine labels and package leaflets should not be removed or damaged;

viii. Each sample should be recorded separately using the sample collection form (for an example see the Annex II). Whenever the required information is not available it should be indicated in the appropriate space on the sample collection form; any observed abnormalities should also be recorded;

ix. Each sample should be identified by a unique sample code, defined on the sample collection form and specified on all original packages belonging to the respective sample (legible and not covering the basic product information). The sample collection form and all packages belonging to one sample should be kept together (e.g. blisters inserted in a dedicated zip-lock plastic bag or envelope marked with the appropriate sample code and trade name of the product). For large surveys, bar-code systems may be helpful and reduce errors;

x. When overt sampling is used, manufacturer's batch certificates of analysis should be collected with samples, if available, and kept with the sample collection form;

xi. Storage conditions at the site (temperature, humidity, access of light, any other observation) should be described in the sample collection form. When overt sampling is used samples collectors can measure temperature if not controlled in the site. Mystery shoppers can estimate and record the temperature;

xii. Samples should be collected and kept under controlled conditions in line with the product label requirements. The cold chain has to be maintained, where required. Samples should be kept protected from light, excessive moisture or dryness. Safety measures against theft should be put in place; medicine boxes should be kept in a locked area.

The time period, within which samples should be collected and the deadline for sending the last sample to the testing laboratory, should be clearly indicated in the procedures and followed.

Normally samples of collected medicines should be paid for by sample-collectors. The exception to this is in case where there is approved written permission to take samples from

any facility without payment. The cost of collected samples needs to be taken into account when determining the numbers of samples to be collected.

Sample collectors should be mindful of the stock of sampled products in outlets, and potential difficulties of replenishment of sampled medicines through the supply chain, so as not to jeopardize the availability of these medicines to patients. If there is a risk of product shortage, after sampling, replacement of the sampled amount should be arranged immediately after the study, or, less desirably, collection of that particular product in that outlet should be omitted.

In case of studies seeking the proportion of poor-quality medicines sold to patients, outlet product-specific sales volumes may be necessary. Collection of these data can be conducted after sampling, especially when the mystery-shopper approach is used, and sellers should be informed about the surveillance study.

Sampling Tools/ Materials

i. Ziploc bags
ii. Labels
iii. Markers
iv. Containers
v. Sample Collection forms
vi. Hand disinfectant
vii. Notebooks and pens
viii. Masking Tapes
ix. Coolers, Ice packs for collecting samples of temperature sensitive products
x. Others

5.2 Overt sampling versus mystery-shopper approach

The decision on who should collect samples will depend on the study objectives, regulatory status of the target medicines and what is known about the knowledge and attitude of sellers (whether he/she knows that the outlet is selling poor-quality medicines and understands the health, legal and ethical implications). If outlet staff are anxious to avoid poor-quality medicines and are informed about the study objectives, overt sampling with feedback would allow more data to be collected on poor-quality medicines and their risk factors and lead to direct improvement in the medicine supply. Overt sampling may be the only possible method in some circumstances, such as if samples are collected where people are seen first by clinicians or in the public sector.

There are instances where within a single outlet there will often be several different brands of the same medicine at different prices aimed at different market segments. In such cases a covert, mystery-shopper approach may be appropriate. The identity and purpose of the buyer should not be generally known by the outlet being evaluated. Sampling is done by an outsider as it may not be safe for people living in the same wider community to act as purchasers. In contrast, in some remote rural locations, it would be difficult for someone who is not local to request medicines as this would cause suspicion. The safety of those acting as mystery shoppers should be considered, the risk assessment performed and instructions appropriate to local conditions developed.

The mystery shopper mimics a "normal shopper" for the community in which the outlet is located and should dress, speak and behave appropriately for the community. They should use a standard scenario, e.g. pretending to be a visitor from another part of the country who needs some medicines for a specified disease, for a specific reason and for a stereotyped patient. The mystery shopper should be prepared to explain the real purpose of the visit to protect himself/herself in case that his/her identity is revealed. After leaving the surveillance place the mystery shopper should record details of the purchase. Price, name of the provider/outlet, estimation of temperature at the place should be documented as well as conditions of the purchase, e.g. how many people were in the outlet, how long it took, what was the interaction between the mystery shopper and outlet staff, was it easy to convince the provider to sell medicines, and other information requested by the study objectives. Collected medicines should be properly identified and stored, e.g. in a plastic bag labelled with the name of the outlet.

The mystery shopper should brief the team leader for the surveillance area after return from each outlet. The focal person should transcribe the reported interaction with translation as appropriate. Translators should use a meaning-based translation method, rather than a literal or interpretative approach. The original text with translation should be double-checked for accuracy by other members of the team and kept.

5.3 Storage and transportation of samples

Storage and transportation of the samples to the testing laboratory should be done according to Good Storage Practice and Good Distribution Practice Guidelines. Handling of samples should be done as quickly and straight as possible so as not to jeopardize the quality of collected samples.

i. Storage and handling conditions of samples should comply with all national regulatory procedures.
ii. Storage conditions for the pharmaceutical products to be sampled should be in compliance with the recommendations of the manufacturer.
iii. Storage areas should be clean and free from accumulated waste and vermin. Sample
iv. Collectors must ensure that premises and storage areas are cleaned regularly.
v. There should also be a written program for pest control in sample storage areas. The pest control agents used should be safe and there should be no risk of contamination of sampled pharmaceutical products. There should be appropriate procedures for the clean-up of any spillage to ensure complete removal of any risk of contamination of samples.
vi. Receiving and dispatch bays should protect pharmaceutical products from adverse weather condition. Receiving areas should be designed and equipped to allow in coming samples to be cleaned if necessary before storage. (MCAZ Good Wholesaling Guidelines)
vii. Medicines and other health product samples should be stored separately from other products likely to alter them and should be protected from the harmful effects of light, temperature, moisture and other external factors.
viii. Medicines and other health products should be handled and stored in such a manner as to prevent spillage, breakage, contamination, cross-contamination and mix-ups.

ix. The samples should be kept in their original packaging and under storage conditions as specified on the label; freezing should be avoided and, where required, the cold chain should be retained.

x. All samples should be packaged adequately and transported in such a way as to avoid breakage and contamination during transport. Any residual space in the container should be filled with a suitable material.

xi. In case of temperature-sensitive medicines, calibrated temperature data loggers should be included within shipments to document adequate temperature in prolonged transit. The temperature should be maintained between 2oC and 8oC suitable for the storage of cold chain medicines.

xii. A covering letter, copies of sample collection forms and, if available, copies of manufacturer's batch certificate of analysis should accompany the samples.

xiii. In the case that sample collectors are not transporting samples directly to the testing laboratory, samples with the accompanying documents should be sent by a courier service or as determined by the PMS management team. For each shipment it should be clearly "indicated that samples are sent for laboratory testing purposes only, will not be used on humans or animals, have no commercial value and will not be placed on the market". Copies of sample collection forms and, if available, copies of manufacturer's batch certificates of analysis should also be sent to the survey coordinator or person preparing the survey report.

5.3.1 Normal storage conditions

Storage in dry, well-ventilated premises at temperatures of 15–25°C or, depending on climatic conditions, up to 30°C.
Extraneous odors, other indications of contamination, and intense light must be excluded.

5.3.2. Defined storage instructions

Drug products that must be stored under defined conditions require appropriate storage instructions. Unless otherwise specifically stated (e.g. continuous maintenance of cold storage) deviation may be tolerated only during short-term interruptions, for example, during local transportation.
Freezing is defined as temperature thermostatically controlled between -25°C and -10°C
Refrigeration is defined as temperature thermostatically controlled between 2°C and 8°C
Cold Place is defined as temperature that does not exceed 8°C
Warm is temperature between 30°C and 40°C
Excessive heat is temperature above 40°C

5.3.3. Interpretation of Labelling of Storage conditions:

Labelling includes all labels and other written, printed, or graphic material on the immediate container of the medicine or on any package or wrapper in which it is enclosed EXCEPT outer shipping container.

"Label" describes or refers to the labelling on the immediate container of the medicine.

The use of the following labelling instruction is recommended on the label: "Do not store over 30°C" means from +2°C to +30°C

"Do not store over 25°C" means from +2°C to +25°C

"Do not store over 15°C" means from +2°C to +15°C
"Do not store over 8°C" means from +2°C to +8°C
"Do not store below 8°C" means from +8°C to +25°C
Labelling which states "Protect from moisture" means the medicines or other health products should be stored in a container with no more than 60% relative humidity. The medicine or other health products should be provided to the patient in a moisture resistant container.

Labelling which states "Protect from light" must have the medicines or other health products provided to the patient in a light-resistant container.

5.4 Risk based approach to testing

Depending on the objectives of each sampling and testing activity, implementing a tiered approach to testing can drastically reduce the number samples to be collected and the types of tests to be performed without affecting the overall quality of post-marketing surveillance. For instance, if the objective of a specific sampling and testing activity is to assess the stability of medicines at different levels of supply chain (i.e., storage conditions), then it may not be necessary to conduct full compendial testing at each level of the system. If identification, disintegration, and dissolution tests were determined for samples at the central level, samples at the district level may only benefit from testing related substances rather than repeating the previously conducted tests. On the other hand, if the initial screening of the sample from the district level showed discoloration, it may not be necessary to conduct additional compendial testing of the sample.

5.4.1. The Three Level Approach to testing

Three-Level Approach proposes that testing can occur at three levels: in the field, initially through visual inspection; then through field-based tests (e.g. Raman Spectroscopic methods); and finally at the laboratory as required (using compendial or other methods accepted by the MCAZ).

5.4.1.1 Visual Inspection

Simple visual inspection may identify important characteristics related to product quality (registration status, expiry, product packaging, etc.) or issues with the physical characteristics of the dosage form (presentation, color, texture, and viscosity, etc.). Testing at this level can be primarily performed in the field at the point of sampling and can be used to identify falsified, substandard, unregistered, or incorrectly labeled medicines. For example, if a box of aspirin is discolored and moldy, immediate action is warranted rather than additional field screening or compendial testing. This initial screen should be mandatory and performed on all collected samples. Failed samples can, in some cases, be omitted from further testing, which reduces the costs associated with post-marketing surveillance.

Visual inspection can also include an assessment of the product label, packaging, and presentation. Inspectors may review the batch number, scientific name, company logo, number of units per container, dosage form, strength, manufacturer address, presence of a package insert, integrity of packaging, color, texture, presence of particulates, and other characteristics. Inspectors should have access to the online medicines registers or other visual inspection tools is critical to effectively supporting the detection of quality issues at

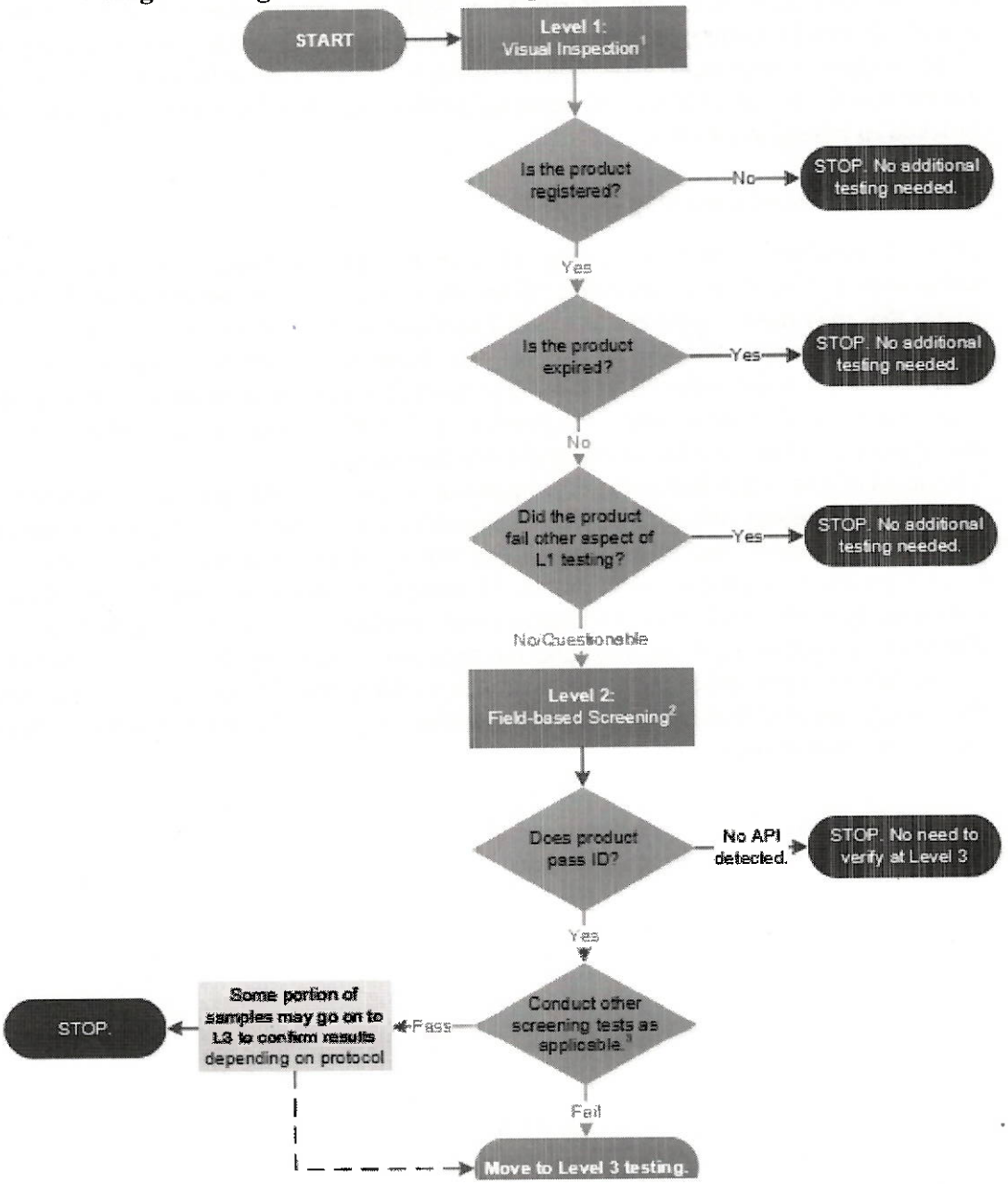
Level 1. Products that fail some aspect of visual inspection should be discussed with the regulatory authority to determine appropriate action. In some cases, the regulatory authority may choose to seek clarification with the manufacturer, proceed with other aspects of quality testing, or take other decisions based on the results presented at Level 1. If the product passes visual inspection or if a determination cannot be made (e.g., deviations are not clearly discernable against expected product presentation), then the product should proceed to testing at Level 2.

5.4.1.2 Field based screening (Level 2)

Level 2 involves analytical testing of product quality using field-based screening technologies. Field-based screening technologies can identify potential product quality issues that may not be apparent at Level 1 and can further reduce the number of samples that require compendial testing (Level 3). Suspicious samples identified by visual inspection may undergo further screening (Figure 2) using one or more advanced screening tests, such as thin-layer chromatography and Raman and/or near infra-red (NIR) spectroscopy (using portable or handheld spectrometers).

This level of test is qualitative to semi-quantitative and, depending on the capability of the screening technology utilized, provides information on the identity of the active ingredient, possible degradation, and/or impurities. Depending on the objective of the sampling and testing protocol, a product that passes identification and other applicable field-based screening provides sufficient information and eliminate the need for additional testing. Based on the screening tools used and the tests performed, the regulatory authority may choose to send a portion of the passed samples for compendial testing (Level 3) to confirm the results. Samples that fail field-based screening tests may be retested at the compendial level to confirm results.

Flow diagram for guidance on visual inspection and field based screening



5.4.1.3 Compendial Testing

Compendial testing provides the most extensive information on product quality, but it is also the most complex, expensive, and time-consuming type of testing. Using a risk based approach in the development of the study protocol, collection of samples, and testing of samples through the Three-Level Approach can reduce the number of samples that need to be tested using compendial methods, and can therefore reduce the costs associated with conducting sampling and testing activities. Compendial testing should be carried out on suspected samples that fail field-based screening tests and, depending on the protocol, on

a portion of samples to confirm the results from Level 2. The use of pharmacopeial methods or other validated methods approved by the NRA is recommended. Note that if a product fails a test at Level 2 (for example, the sample does not pass disintegration), the same test should be performed at Level 3 using compendial methods before initiating tests for other quality attributes. If the result from Level 2 is confirmed at Level 3, then no further testing is needed. If, on the other hand, conducting the same test using compendial methods does not confirm the result from Level 2 testing, it is recommended that the analyst proceed with the suggested prioritization of compendial tests.

Additionally, for products procured by the Global Fund or similar organizations with sound quality assurance measures in place (i.e. products are only procured from WHO prequalified or stringent regulatory authority approved sources and pre-shipment lot testing is conducted), a selection of appropriate compendial tests may be considered based on the where in the supply chain samples were collected. For instance, if samples from a Global Fund procured lot were collected from the port-of-entry, then performing an assay of the sample may be sufficient. Similarly, if the same lot of product is sampled further downstream in the distribution chain (e.g., from the public health facility) then assessing the stability of the product by performing related substance/impurities testing may suffice.

5.4.1.4 Testing Laboratory

It is important that only quality control laboratories that are ISO/IEC 17025 accredited or WHO pre- qualified laboratories, which demonstrate capability to produce reliable testing results of international repute and reproducibility, are used in PMS studies. The MCAZ laboratory would be used for testing all medicines

The laboratory works in compliance with WHO *Good practices for pharmaceutical quality control laboratories* (WHO TRS No. 957, 2010. Annex 1). Preferably a WHO prequalified laboratory or a laboratory where other evidence of equivalent working standards is available; Like ISO/IEC 17025 accredited lab.

i. The laboratory is capable and competent to perform tests required by the testing protocol
ii. The laboratory has sufficient capacity and agrees to test the required number of samples within the specified period for the cost within the available budget.

The choice of the testing laboratory should be explained in the study protocol. There can be one or more laboratories used for testing of samples collected for the surveillance study and this may depend on the number of samples. If more than one laboratories are involved in testing collected samples, samples should be divided among laboratories in a way that all samples containing the same APIs are assigned to one laboratory. The appropriate arrangement with the laboratory has to be made in advance. Within the usual selection procedure and the resulting agreement, the following should be clearly specified in addition to the usual elements of such agreements (such as test parameters, deadlines, financial arrangements etc.):

i. Medicines and numbers of samples to be tested, tests to be conducted and specifications to be used according to the testing protocol. If there are more testing laboratories selected, a specific testing protocol should be prepared for each laboratory;
ii. Responsibilities of the laboratory during the study as specified in the protocol.

iii. Confidentiality declaration of the laboratory;
iv. Acceptance of a possible audit of the laboratory, access to records and retained samples.

Once an agreement is reached, the study coordinator should inform the focal persons participating in the study about the name and address of the laboratory, the contact person(s) in the laboratory and medicines assigned for testing to the particular laboratory. The laboratory normally starts testing only when all samples containing the same API in the same dosage form are received. Therefore, it is important to adhere to the deadline for sending samples to the testing laboratory.

5.4.1.5 Tests to be conducted

Laboratory testing of samples should be performed according to the testing protocol, which is a part of the study protocol, and should be agreed with the testing laboratory. Depending on the study objectives, target medicines and available resources, the tests to be applied to samples collected in the study may include:

i. Verifying the identity;
ii. Performing complete pharmacopeial or analogous testing;
iii. Performing special or specific tests.

In the case that testing should provide a full picture of the quality of target medicines, it should be performed according to a pharmacopeial or analogous monograph and the following tests are, in principle, included:

i. Appearance, visual inspection;
ii. Identity;
iii. Assay for APIs declared on the label;
iv. Test for related substances; impurities
v. For solid dosage forms – dissolution or disintegration, uniformity of dosage units (by mass or content), fineness of dispersion in case of dispersible tablets;
vi. For liquid dosage forms – pH value and volume in containers/extractable volume and microbial limit test;
vii. For parenteral products – sterility and bacterial endotoxins tests.

Inclusion of uniformity of content for single-dose dosage forms, or sterility and bacterial endotoxins tests, which are costly, time demanding and need more dosage units to be collected, should be considered in relation to target medicines and available resources. It is impossible to achieve 100% certainty about sterility of the product through testing only and inspections and enforcement of compliance with GMP principles may be more efficient tools for verification in some cases.

Packaging of each collected sample, labelling and package leaflets should be inspected visually for any signs of a substandard and falsified (SF) medical products.

Information on labels and in package leaflets can also be checked for quality and completeness of essential information and compliance with requirements and approved product information in Zimbabwe can be verified.

Screening methods do not provide a full picture of the quality of medicines and may underestimate non-compliant findings in comparison with laboratory testing. However, they enable testing of large number of samples in the field, e.g. to search for SF medicines. It is recommended to verify outcomes of screening by laboratory testing, at least for a random selection of those samples that pass screening and for all those that fail.

5.4.1.6 Test methods and specifications

Test methods and specifications should be selected in a way to best meet the study objectives. In general, when samples from different manufacturers are collected within a PMS study, all samples containing the same APIs in the same dosage form are tested using the same method and specification to enable comparison of samples from different manufacturers. This specification is then used to decide on compliance or non-compliance of tested samples for the purposes of the PMS study. It should be noted that individual manufacturers may use different specifications and different methods for testing of their products.

Non-compliance with the specification selected for the survey does not, therefore, necessarily imply non-compliance with the specifications approved in Zimbabwe but it indicates the need to look at the product and conditions of regulatory approval more closely and further actions should be considered by MCAZ.

Wherever they are appropriate, pharmacopeial methods and specifications should be used. In other cases of PMS study widely accepted pharmacopoeias (such as the International Pharmacopoeia, British Pharmacopoeia or United States Pharmacopeia) may be appropriate. In spite of efforts to harmonize pharmacopoeias there are still many differences. When a monograph for the particular medicine is available in more pharmacopoeias the ability of the respective methods and specifications to reveal quality problems should be considered and the monograph selected accordingly.

If no monograph for the target medicine exists in pharmacopoeias or the existing monographs do not provide for desired tests, a validated method of the laboratory should be used.

5.4.1.7 Receipt and testing of samples by a testing laboratory

When samples are received, the testing laboratory should:

i. inspect each sample to ensure that the labelling is in conformance with the information contained in the sample collection form or test request; an electronic databank (e.g. scanned pictures or photographs of the medicines, such as of the tablets, packaging, and package leaflet) is recommended; store the samples in line with the conditions on product labels, including compliance with any cold chain requirements;

ii Conduct quality testing in line with the testing protocol and in compliance with Good Practices for Pharmaceutical Quality Control Laboratories, including investigation and documentation of each OOS result according to the laboratory SOP. If the OOS result is confirmed, it should be reported without delay to the surveillance study coordinator providing both results and investigation report;

iii Complete analytical test reports/certificates of analysis containing information listed in Annex II. The study coordinator should define the format of the outcome (e.g. separately for each sample or as a tabulated report);

iv keep document/s received with samples, records of testing of each sample including all raw data and retention samples according to the requirements defined by the study coordinator (e.g. for at least six months if the sample complied with the specifications, or for at least one year or until the expiry date, whichever is longer, if it did not comply) and archive data according to the agreed conditions.

5.4.1.8 Data management and publication

To allow proper interpretation of data obtained during collection and testing of samples, the data should be summarized and well-arranged in a database (using Excel sheets or software for epidemiological studies), linking each sample with all the gathered data and ensuring consistency and security. Any errors should be avoided. For analysis of large sets of data statistical software may be used. If relevant, personal identification of individuals who participated in the study (buyers, sellers, etc.) should be entered in the database using codes only.

The Study Coordinator should be informed forthwith about confirmed OOS results to be able to investigate in line with regulatory practice and legislation with the relevant manufacturer or other party. It should be kept in mind that if testing methods would be in compliance the compendia specification. Once the study results are compiled, evaluated and summarized, it is recommended that PMS management should hold a meeting with appropriate stakeholders to discuss the results and the actions needed before publication.

A detailed PMS report should be prepared including all testing results for collected samples. An example of the outline of the study report content is provided in Annex II. Recommendations for items to be addressed in reports of medicines quality studies can also be found in published literature.

The report should be publicized as widely and openly as possible. The results should provide a feedback on the effectiveness of the QA system and may influence national policies as well as have a direct impact on individuals and public health.

5.4.1.9 Evaluation of Results:

i. The Committee/ body that is responsible for the PMS program and sampling plan should receive the results from the laboratory and advise on regulatory actions. This is also a function of the QMS department.

ii. Each staff responsible for gathering data must summarize the data on the frequency from the PMS study. If there is no new data to report, this should be stated in the summary. If there is a large amount of similar data, it is acceptable to present a statistical analysis of that data.

iii. Additional PMS actions should be identified and followed up. This could involve inspections, further targeted sampling and analysis, or further laboratory analysis

iv. SOP should be in place for proper methods of evaluating results.

5.4.1.10 Report Preparation and Publication:

i. As stated above, a detailed PMS report should be prepared. This process should involve all departments involved in the planning, sampling, screening, analysis, and evaluation within the PMS program
ii. The report should be approved by the Director General of MCAZ and disseminated to stakeholders for comments.
iii. Report should be made available through the website
iv. All relevant Stakeholders, Ministries, Implementing Partners should receive the report annually

6.0 KEY RELEVANT DOCUMENTS

6.1 Guidelines on Quality Control Testing of Antimalarial Medicines at NAFDAC ISO 17025 Accredited Laboratories
6.2 WHO guidelines for sampling of pharmaceutical products and related materials. (TRS No. 929, 2005)
6.3 MCAZ GDP guidelines
6.4 WHO Good practices for pharmaceutical quality control laboratories (WHO TRS No. 957, 2010. Annex 1
6.5 Guidance for implementing risk-based post –marketing quality surveillance in low and middle income countries, 2016

7.0 HISTORY

DOCUMENT HISTORY		
Revision Number	Date Approved	Reason for Change and Amendments
N/A	N/A	N/A

Annex I: Sample collection Form

PMS Study Title: .....

1. Sample code: Zone/Area/Facility/product/serial No (abbreviated name of each to 3 characters)
2. Name of monitoring site (*Zone*): _____
3. Date of collection of sample: _____
4. Name and address of collection site: _____

Type of collection site /point:

HEALTH FACILITY: LEVEL-I	**Public**	**Private**	**HEALTH FACILITY: LEVEL-II**		**Urban**	**Rural**	**Public**	**Private**
Manufacturing Outlets			**Hospitals**	Tertiary				
				Secondary				
National Medicine Distribution Centers (Natpharm)				Primary				
Medicines Distribution Centers				Clinics				
Importers/Distributors			**Community Outlets**	Wholesale pharmacies				
				Retail Pharmacies				
				PPMVs				

SAMPLE INFORMATION	
Name of location/place where sample was taken	
Street address with telephone	
Date of sampling	
Trade or brand name sample	
Generic or INN name	
Dosage strength	
Manufacturer's Batch or Lot Number	
Manufacturing date	
Expiry date	

MCAZ Registration number (if applicable)	
Purchase date (dd/mm/yy), if applicable	
Approximate length of time the sample being at this location.	
Manufacturer name and address	
Dosage form (e.g.ampoules, injection or tablets)	
Pack size (No of products per pack)	
Type of packaging material (primary containers such as strips, PVC or bottles)	
Indicate storage temperature per manufacturer's labeling and instructions	
□Samples were stored in a refrigerated condition which was: □specifically used for medicines and vaccines □found appropriate (with temperature monitor) □required defrosting □clean and cold	□Samples were not stored in refrigerated condition, Please briefly described where and how the Medicine were stored at the facility during the sampling …… …….. …… Reasons why the Medicines were not stored in refrigerated condition: □No refrigerator □Don't know that products should be kept in a refrigerator □Other reason(s), please specify: …… ……
Brief physical/visual description of sample	
GPS Coordinates of the location	
Name of collector(s)/date/sign	1…… 2……

Annex II: Content of the analytical test report/certificate of analysis

1. Name and address of the laboratory performing the sample testing.
2. Name and address of the originator of the request for testing.
3. Number/code of the analytical test report/certificate of analysis.
4. Sample reference number assigned by the laboratory and sample code assigned at the time of sampling (specified in the sample collection form and packages belonging to one sample).
5. Date on which the sample was received.
6. Name of the area/Zone where the sample was collected.
7. Name of sample product (trade name as appears on the label),
8. Dosage form, APIs, strength, package size (e.g. number of tablets in one blister and number of blisters in the secondary packaging, volume in one ampoule and number of ampoules in secondary packaging).
9. Description of the sample (both description of the product and of primary and secondary packaging, type and packaging material of primary container); if there is any sign of bad handling during the transportation, it should be mentioned.
10. Batch number of the sample, expiry date and, if available, manufacturing date.
11. Quantity of units received for the sample.
12. Name and full address of the manufacturer (as specified on the label or in the package leaflet).
13. Reference to the specifications used for testing the sample, including the limits.
14. In the case that a reference substance was used for quantitative determination, the substance should be specified (e.g. British Pharmacopoeia or United States of America Pharmacopeia reference substance or working standard).
15. Results of all the tests performed; for the evaluation and interpretation of results it is useful to request numerical results wherever possible, any observation made during testing and the following details:
    - Appearance
    - uniformity, filling volume for individual units,
    - dissolution test, results for all tablets tested,
    - Assay for content of active ingredient (s)
    - Sterility test
    - average and the relative standard deviation (RSD);
    - Is there OOS result
16. Does its required retesting or the investigation reporting?
17. Date on which the test was completed.
18. Does the sample comply with the specifications set for the PMS study?
19. Signature of the head of the laboratory or authorized person.