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National Agency for Food & Drug Administration & Control (NAFDAC)

Post-Marketing Surveillance (PMS) Directorate

Guidelines for Post-Marketing Surveillance of Medical Products in Nigeria

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Acronyms

API	Active Pharmaceutical Ingredient
cGMP	Current Good Manufacturing Practice
CRH	Certificate of Registration Holder
MAH	Marketing Authorization Holder
IMDRF	International Medical Devices Regulators Forum
NMRA	National Medicines Regulatory Authority
NGO	Non-Governmental Organization
NAFDAC	National Agency for Food Drug and Administration and Control
NQAP	National Quality Assurance Policy
OOS	Out of Specification
PCN	Pharmacist Council of Nigeria
PMI	Presidential Malaria Initiative
PMS	Post Marketing Surveillance
PPMV	Proprietary Patent Medicine Vendor
PQM	Promoting the Quality of Medicines
QA	Quality Assurance
SF	Substandard and Falsified
SOP	Standard Operating Procedure
USP	United States Pharmacopeial Convention

1.0. Introduction

Post Marketing Surveillance (PMS) is a regulatory function carried out by National Medicines Regulatory Authorities in a country. PMS of pharmaceutical products involves assessing the quality of medicines to generate reliable scientific evidence required to take regulatory action to protect public health. It continuously monitors the quality of marketed medicines throughout their shelf life and at all levels of the supply chain.

The quality of medicines refers to its level of suitability for intended use by the consumer. 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 leaflets. The national quality assurance policy is available to ensure the maintenance of quality from the manufacturer to the end user. To ensure that the quality of medicines is maintained/monitored while being distributed, USP Plus/PQM sponsored a workshop to provide a platform for NAFDAC and relevant stakeholders to discuss and emphasize the need for best practices in post-marketing surveillance of pharmaceutical products.

Note: These Guidelines should be read in conjunction with all relevant IMDRF guidance documents.

The regulatory activities of NAFDAC that ensure the quality of medicines in Nigeria include:

- Authorization/registration/licensing of medicines for marketing based on the assessment of safety, efficacy, and quality.
- Inspection of manufacturers of the medicines for compliance with the principles of Good Manufacturing Practices (GMP); and approval of products' information.
- Import control of medicinal products.
- Inspection of premises for the storage and distribution of medicines.
- Post-marketing surveillance.
- Pharmacovigilance.
- Regular inspections of manufacturers, wholesalers/distributors/retailers and quality control/ testing laboratories
- The analysis of samples of medicinal products.
- Regulation of advertising and promotion.
- Provision of independent information to healthcare providers, patients, and the public.
- The quarantine, recall, and destruction of substandard and falsified medical products.
- Enforcement of National medicine legislation.

1.1. Purpose of PMS Guidelines

The purpose of these guidelines is to strengthen the NAFDAC system for effective Post Marketing Surveillance of pharmaceutical products such as medicines and medical devices to ensure that only quality and safe medicinal products are distributed, advertised, sold, and used throughout the country. This is in line with ICH Q10 (Pharmaceutical Quality System) which emphasizes the need for a robust system that ensures product quality throughout its lifecycle. Effective implementation of PMS Guidelines will enable NAFDAC to generate scientific evidence on the quality of medicines and medical devices for improved health outcomes. Nigeria must sustain high-quality and scientifically credible safety and efficacy data for these vital health commodities to enhance evidence-based decision-making that impacts public health.

1.2. Scope:

The PMS plan is designed to cover a wide range of medicinal products marketed in Nigeria to strengthen and improve their quality and safety. This aligns with ICH Q10 (Pharmaceutical Quality System) thereby ensuring that PMS processes involve continuous improvement and emphasize the quality and safety of medical products.

Ensuring that there is adequate funding is vital during the PMS planning. In a situation where resources are limited, the PMS program can focus on medicines and parameters that pose a higher risk to patients by applying risk analysis during the planning phase in line with ICH Q9(R1) (Quality Risk Management). Collaboration with relevant partners and sharing of resources including testing capacities, experiences, and information can enhance the effectiveness of the PMS program.

1.3. Post-Marketing Surveillance of Medical Products

Post-marketing surveillance of Medical products provides an important source of information on the quality of Medical products available in the market. The surveillance program must be organized in such a way that will involve stakeholders such as international organizations, procurement agencies, NGOs, 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 pharmaceutical products in the country hence the need to prioritize medicines based on the perceived risk to the consumer using a risk-based approach in line with ICH **Q9(R1)** (Quality Risk Management) which supports the application of risk-based approaches in monitoring the quality of products, helping NAFDAC focus on products and parameters that pose the highest risk to

consumers. The information obtained from PMS activities is vital to enhance and maintain the quality assurance system in Nigeria.

NOTE: All Certificate of Registration Holders(CRH) of medical devices in the country are required to keep distribution records of where the devices have been supplied, including distributor centers and hospitals, to:

i. expedite any recalls of the medical devices, and
ii. identify manufacturers of each batch of devices.

Data collection on the quality of medicines, if properly executed, interpreted, and used, will be useful for the planning of effective interventions and taking appropriate regulatory actions 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 availability of resources, amongst others. Post-marketing surveillance surveys on the quality of medicines are costly, and available resources may restrict the number of samples to be collected, testing parameters, techniques to be used for analysis, or the number of staff available to analyze the samples.

To sustain regular PMS activities in Nigeria, NAFDAC has established a suitable and practical organizational structure that ensures the execution of effective surveillance activities all year round. Steps 2 to 13 will be necessary for the continuous execution of the PMS program. The existing PMS Division in NAFDAC is solely dedicated to conducting PMS activities.

1.4. Glossary

The definitions below apply to the words and phrases used in these guidelines. Although an effort has been made to use standard definitions as far as possible, they may have different meanings in other contexts and documents.

Agency	**National Agency for Food and Drug Administration and Control**
Batch	A defined quantity of pharmaceutical products processed in a single process or series of processes so that it is expected to be homogeneous
Batch Number	A distinctive combination of numbers and/or letters that uniquely identifies a batch, for example, on the labels, its batch records, and corresponding certificates of analysis.
Consignment	The quantity of pharmaceutical products supplied at one time in response to a particular request or order. A consignment may comprise

	one or more packages or containers and may include pharmaceutical products belonging to more than one batch
Container	The material employed in the packaging of a pharmaceutical product. Containers include primary, secondary, and transportation containers. Containers are referred to as primary if they are intended to be in direct contact with the product. Secondary containers are not intended to be in direct contact with the product.
Contamination	The undesired introduction of impurities of a chemical, microbiological nature, or of foreign matter, into or onto a starting material, intermediate, or pharmaceutical product during handling, production, sampling, packaging or repackaging, storage or transportation.
Controlled or hazardous pharmaceutical products	Poisons, narcotics, psychotropic products, inflammable or explosive substances, and radioactive materials.
Counterfeit Medical product	A Medical product that is deliberately and fraudulently mislabeled with respect to identity and/or source. Counterfeiting can apply to both branded and generic products and counterfeit pharmaceutical products may include products with the correct ingredients, with the wrong ingredients, without active ingredients, with an incorrect quantity of active ingredients, or with fake packaging.
Cross-contamination	Contamination of a starting material, intermediate product, or finished pharmaceutical product with another starting material or product during production, storage, and transportation.
Expiry date	The date given on the individual container (usually on the label) of a pharmaceutical product up to and including the date on which the product is expected to remain within specifications if stored correctly. It is established for each batch by adding the shelf-life to the date of manufacture
Falsified Medical product	Any pharmaceutical product with a false representation of: Its identity, including its packaging and labeling, its name or its composition as regards any of the ingredients including excipients and the strength of those ingredients Its source, including its manufacturer, its country of manufacturing, its country of origin or its marketing authorization holder; or its history,

	including the records and documents relating to the distribution channels used
Good Manufacturing Practices (GMP)	That part of quality assurance ensures that pharmaceutical products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization
Labelling	Process of identifying a pharmaceutical product including the following information, as appropriate: name of the product; active ingredient(s), type and amount; batch number; expiry date; special storage conditions or handling precautions; directions for use, warnings, and precautions; names and addresses of the manufacturer and/or the supplier
Medicine	A medicine refers to a pharmaceutical drug or product (see NQAP 2015)
Pharmaceutical product	Any product intended for human use or veterinary product intended for administration to food-producing animals, presented in its finished dosage form, that is subject to control by pharmaceutical legislation in either the exporting or the importing state and includes products for which a prescription is required, products which may be sold to patients without a prescription, medical devices, biologicals and vaccines.
Post Market Surveillance (PMS)	The regulatory function of National Medicines Regulatory Authorities involving the assessment of the 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.
Regulated products	Regulated products are products that are subject to mandatory regulatory requirements in the country or region where it is manufactured or imported. These products could be high- or medium-risk and include food, drugs, cosmetics, medical devices, detergents, bottled water, and chemicals.
Recall	A process for withdrawing or removing a pharmaceutical product from the distribution chain because of defects in the product, complaints of serious adverse reactions, and or concerns that the product is or may be counterfeit. The recall might be initiated by the manufacturer, importer, wholesaler, distributor, or the Agency

Sample	A pharmaceutical product, medicine, or medical device in a 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. (See Guidelines on Quality Control Testing of Antimalarial Medicines at NAFDAC ISO 17025 Accredited Laboratories
Quality assurance	A wide-ranging concept covering all matters that individually or collectively influence the quality of a product. It is the totality of the arrangements made to ensure that pharmaceutical products are of the quality required for their intended use.
Quality system	An appropriate infrastructure, encompassing the organizational 53 GLOSSARY NAFDAC GOOD DISTRIBUTION PRACTICES GUIDELINES FOR PHARMACEUTICAL PRODUCTS 2016 structure, procedures, processes and resources, and systematic actions necessary to ensure adequate confidence that a product (or services) will satisfy given requirements for quality.
Shelf-life	The period during which a pharmaceutical product, if stored correctly, is expected to comply with the specification as determined by stability surveys on a number of batches of the product. The shelf-life is used to establish the expiry date of each batch.
Standard operating procedure (SOP)	An authorized, written procedure giving instructions for performing operations not necessarily specific to a given product but of a more general nature (e.g. equipment operation, maintenance and cleaning, validation, cleaning of premises and environmental control, sampling and inspection).
Storage.	The stowing of pharmaceutical products up to the point of use.
Storage temperature	The temperature ranges indicated on the product label and recommended for storage of a product.
Time- and temperature-sensitive	Any pharmaceutical good or product which, when not stored or transported within predefined environmental conditions and/or within

pharmaceutical product (TTSPP).	predefined time limits, is degraded to the extent that it no longer performs as originally intended.
Transit	The period during which pharmaceutical products are in the process of being carried, conveyed, or transported across, over, or through a passage or route to reach the destination
Transport	Moving pharmaceutical products between two locations without storing them for unjustified periods.

2.0. Objectives

2.1. General Objective

The objective of this guideline is to outline the steps to consider when preparing and conducting a survey on the quality of pharmaceutical products in Nigeria. Surveillance should be conducted regularly based on risk assessment, available resources, and personnel capacity. It should conclude with a meeting involving partners and stakeholders to reveal and discuss the results.

2.2. Specific Objective

To enhance evidence-based regulatory decision-making, improve population health outcomes, and provide scientific evidence on medicine quality in line with ICH Q10 (Pharmaceutical Quality System).

3.0. Protocol for survey

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

4.0. Survey management and time frame

The management team should be responsible for coordinating and managing the PMS activities, especially quality monitoring surveys, through a robust quality management system.

NAFDAC should approve the PMS survey plan before it commences. The responsibilities and tasks of persons having key roles in the PMS survey (e.g. survey coordinator, team

leader in individual areas) are clearly outlined. There should be a clear communication link between the different departments within the PMS Division.

Before the initiation of the program, the personnel heading the different aspects of the PMS activity shall meet and gain a clear understanding of the responsibilities of the various steps from 2 to 13 such as product selection, site selection, collection and handling samples, data collection and interpretation, data storage, etc. All personnel involved in PMS activities should be trained on the requirements of PMS in line with ICH Q10 (Pharmaceutical Quality System). They should have the appropriate experience and competence before commencing their tasks. Training should be based on written standard operating procedures (SOPs).

- Personnel should receive initial and continuous training relevant to their roles and responsibilities, based on written procedures and in accordance with a written training program. The responsible persons should also maintain their competence in PMS through regular training.
- In addition, training should include the aspects of product security, as well as the aspects of product identification, detection of counterfeits, and avoidance of counterfeits.
- 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.
- A record of all training should be kept, and the effectiveness of training should be assessed and documented (see NAFDAC GDP Guidelines, 2021)

Before starting a quality survey, it is important to clearly state the objectives and provide detailed purposes for the survey. The PMS survey should address specific public health priorities, quality assurance, 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 survey should recommend appropriate regulatory actions that address public health concerns.

- Due to cost implications and the 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 survey and proffer recommendations and follow-up actions.

Areas to be considered during the planning stage of a quality survey include the following:

i. **The quality of the target pharmaceutical products**
   - The information may be sought in scientific literature, alerts on medicine quality, and published surveys. It is important to gather information from inspectors, assessors, laboratory, and pharmacovigilance experts and design the survey in collaboration with a multidisciplinary team as per ICH Q10 (Pharmaceutical Quality System).

ii. **The distribution and supply system of the target medicines**
   To design the survey 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 survey objectives, this is in line with ICH Q9(R1) (Quality Risk Management) supports a risk-based approach. Complex supply chains pose a higher risk of quality deterioration and should be prioritized in market surveillance activities. Information on distribution or supply chains should be available to NAFDAC, the Ministry of Health, PCN, other MRAs, and other related governmental organizations.

iii. **Health-seeking behavior for the target medicines**
   - For some surveys, it may be important to understand where different categories of patients tend to buy their medicines and the kind of products they buy. In many countries, the pharmaceutical market is highly segmented, with distinct segments catering to individuals with different income levels. For example, the wealthier people may go to pharmacies or private clinics, the poorest go to street peddlers or patent medicines stores, and people of middle income may go to hospitals. There will also be brands of the same product at different prices to target different market segments. If such information is needed, an initial pre-surveillance survey should be conducted.

iv. **Patients' exposure to the target pharmaceutical products**
   Medicines with high consumption volumes should be prioritized in market surveillance activities. It may be difficult to obtain exact consumption volumes in Nigeria, but some estimates based on distribution volumes or information from various disease control programs can be used.

v. **Brands of the target pharmaceutical products available in the surveillance, identified areas or selected outlets.**

If the objectives of the survey 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 survey asking for a product list at the selling points may help to collect the data needed to plan the survey better.

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

Other aspects to include in the survey are:

- The variables and endpoints that will be used to answer the surveillance questions e.g., the Quality Parameters, etc.
- The surveillance approach or methodology to be used
- Sample size and units of observation
- Source of data i.e., levels of data collection at various facilities etc.
- The data collection plan and tools
- Timeline estimation of the survey - what is the expected duration of the survey
- All data analyses and statistical tests planned
- The content and timing of reports
- Dissemination of the report
- Regulatory actions to be taken
  - Publication of reports

Table 1.0: Sample plan of survey activities

Activity	Time frame	Responsible Person
Constitution of a technical working group		
Selection of areas/regions and medicines to be surveyed		
Preparation of survey protocol		
Finalization of testing protocol in agreement with testing laboratories		

Preparation of a detailed sampling plan		
Preparation and pilot test of data collection instructions and procedures, if needed		
Training and supervision of sample collectors		
Collection of samples		
Database of information on collected samples (including scanned pictures or photographs of the dosage form, labels, and package leaflet)		
Visual screening of samples and identification of samples		
Transport of samples to testing laboratory/laboratories in a manner that assures sample chain of custody and maintaining samples in a state of control, to preclude compromising the samples during shipment or transfer to the laboratory		
Testing of samples		
Compilation of results		
Data analysis		
Preparation of draft report		
Presentation of the report to relevant stakeholders and discussion of results for regulatory actions needed		
Report finalization		
Dissemination and publication of the results		

5.0. **Methodology**

All surveys should be conducted according to a predefined survey protocol in line with ICH E6 (Good Clinical Practice) which emphasizes the importance of adhering to a well-documented protocol to ensure the scientific integrity of a survey. Sampling is the most critical part of a PMS activity; it determines the effectiveness of the Survey results.

Biased sampling is a major cause of ineffective PMS surveys and may lead to inaccurate results and recommendations. PMS results offer feedback on the effectiveness of the QA system and may impact national policies as well as a direct effect 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 Survey should be made available to all relevant personnel, and there should be evidence of a clear understanding of these materials and processes and procedures in line with ICH Q10 (Pharmaceutical Quality System). It is recommended that sound statistical approaches be used in sampling to make it scientific and representative of the entire population of the Survey.

Previous studies, if any, should be used to gather more information relevant to the Survey. Some examples of questions to be asked may include but are not limited to:

- What percentage of sampled medicines failed quality testing?
- What quantity of sampled medicines failed quality testing at different levels of the regulated distribution chain and in the informal market?
- What quantity/percentage of medicines sampled at different geographical regions failed quality testing?
- What quantity/percentage of samples of medicines produced in Nigeria and samples of imported medicines failed quality testing?
- Which specific quality test does the selected medicines fail?
- Are any of the deficiencies critical, i.e., could they substantially affect treatment efficacy and/or cause harm to patients?
- In line with the risk-based approach, what is the registration status of sampled medicines, and what percentage of registered medicines failed quality testing?
- What supply chains distribute poor-quality medicines and what market segments do they share? Are there any indicators of poor storage and distribution conditions that influence the quality of sampled medicines? Are there poor-quality medicines in the selected area, border checkpoint, etc.? What is the proportion of poor-quality medicines being sold?

Does the proportion of poor-quality medicines exceed a predetermined level (if any)?

- As the quality changed for a medicine, or medicine category, or in an area (in case of repeated random surveys with consistent design)? What action was taken from the previous observations or outcome?
- What impact does the observation or outcome patients or population health?
- Was there a systematic evaluation of the previous issues, and how was it resolved?

Is there a reporting mechanism to inform WHO and manufacturers or send out safety alert notice?

5.1. Selection of areas to be sampled

Different geographical areas should be selected for the PMS Survey unless the objectives explicitly justify targeting a specific area. Samples should not be collected only in the capital city, as situations in rural and sub-urban areas are often very different, this is in line with ICH Q9 (Quality Risk Management) which encourages a risk-based approach when selecting sampling areas. Depending on the Survey objectives, the following variables may be considered for the selection of sites for the PMS Survey:

- Population density
- Incidence/prevalence of the disease for which the target medicines are indicated
- 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, and areas where the formal supply chain is.
- health services are limited, in areas where NAFDAC has little or no resources to monitor the distribution of medicines
- Number of surrounding villages
- Income level of the population in the target areas
- Areas with complex distribution systems.

Note: The MedRS tools contain relevant risk factors that can be used to determine relevant geographical areas to be included in each surveillance activity.

5.2. Selection of medicines to be surveyed

A risk-based approach in line with ICH Q9(R1) (Quality Risk Management), should be deployed to establish the rationale for the selection of medicines which may include:

- Probability of the occurrence of a quality problem. This may consider risk factors such as the complexity of the manufacturing process, stability, etc.
- Impact of the occurrence of quality problem. This may include exposure of patients to medicine and the seriousness or potential health hazards associated with it used amongst others.

The selection criteria could include epidemiology, geography, accessibility, QA issues, product specification, public health, enforcement, consumer complaints, and herbal products.

The category of pharmaceutical products to be studied may be characterized based on 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 a collection of commonly used products is required, a pre-survey investigation of treatment-seeking behavior may be necessary.

Working collaboratively with other sectors, such as public health programs, the Federal Ministry of Health, healthcare program centers, and pharmacies, may help to identify commonly used products in line with ICH Q10 (Pharmaceutical Quality System) which emphasizes collaboration with stakeholders to ensure the effective planning and execution of surveys.

The MedRs tool may be used to reduce the number of medicines to be included in the survey when resources are limited and there is a need to prioritize the survey to products that pose the most risk to the population.

5.3. Selection of sample collection sites

5.3.1. Types of sample collection sites

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

- Government health facilities
  - ❖ Federal Central Medical Store
  - ❖ Central Medical Store(s) CMS from the 6 Geopolitical Zones
  - ❖ Selected Health Facilities in urban and rural areas in the country such as primary, secondary, and tertiary health institutions.

- Private health facilities
  - ❖ Manufacturers
  - ❖ wholesale Centers
  - ❖ Private hospitals/ Clinics

- ❖ Pharmacies
- ❖ PPMVs
- ❖ First Line Buyers

- Non-governmental Organizations (NGOs)

The other type of classification for sample collection sites is 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.

Level 2	-	Wholesalers/distributors
Level 3	-	Pharmacies, PPMVL and other regulated retailers, dispensing facilities, hospitals, health centers, sub-health centers, clinics, treatment centers, health posts, community health workers.
Level 4	-	Virtual outlets e.g., online sales of medicines
Level 5	-	Informal/unauthorized outlets selling medicines outside the approved distribution system, e.g. kiosks, street vendors, grocery shops, drug stores, and unlicensed patent stores.

Sample collection should be performed in both the public and private sectors as well as in the "informal market" which includes unlicensed outlets. Depending on the objective of the survey, samples may also be collected from unlicensed outlets for special purposes. Types of sites for sample collection should be chosen to best fulfill the survey objectives, and the selection process should be clearly explained. The 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 medicine's 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 the supply chain management.
Samples collected at entry points to the market may be less affected by storage and distribution conditions encountered during distribution within the country. 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 handled if the results are quickly available.

The sites where samples will be collected in the survey should be identified according to address and type of facility. Good local knowledge of the distribution and supply chain is required. NAFDAC should develop a list of the outlets within the distribution chain.

5.3.2. Sampling designs

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

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

5.3.2.1. Convenience sampling

Convenience sampling is a non-probability sampling technique based on the judgment of the PMS Survey 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 survey objectives. Whenever convenience sampling is used, it is important to report how the sites were identified and the types and proportions of pharmaceutical outlets represented in the selection.

Convenience samplings are simple and do not necessarily need complete lists of outlets in defined areas which may be difficult to obtain especially

for mobile outlets. However, they are inherently prone to biases which must be considered when interpreting the survey outcomes. It is a technique predominantly used for selection of sample collection sites by Medicine regulatory authorities. To utilize resources most efficiently, NAFDAC 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 the medicines are distributed to the site, transport conditions, storage conditions and handling of products in the site, and experience of NAFDAC 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 evidence to support regulatory actions or signal a quality problem. If convenience sampling does indicate that a medicine has a 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.

5.3.2.2. **Simple 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. The formula for the calculation of a sample size for random sampling can be found in the relevant literature. The drawbacks of random sampling include the need for large sample sizes, complete lists of target outlets' locations, and additional labor and time costs. In addition, it is essential to recognize that a random sample will only yield reliable and useful information if the selection of outlets and the sampling within each outlet align with the primary objectives of the survey. For instance, it would not be helpful to randomly check the quality of medicine in private hospitals when most patients get their medicine from public hospitals. Similarly, using plainclothes shoppers to randomly sample a medicine that the store staff knows should not be sold to customers would also not be useful.

Subsequently comparing estimates using the same sampling method should be valid and will allow the evaluation of interventions.

5.3.2.3. **Stratified random sampling**

Stratified sampling is a probability sampling technique wherein the Agency divides the entire group of facilities into different subgroups (layers/strata), and then randomly selects the final subjects proportionally from the subgroups. Stratified sampling can be used to adjust for potential differences, e.g. type of products or geographical area where products are obtained 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 in proportion to the number of outlets will be more efficient than simple random sampling. The randomization procedure must use formal random number tables or statistical calculations.

5.3.2.4. **Lot Quality Assurance Sampling**

This methodology may be considered when dealing with the PMS of other relevant medical products.

5.3.2.5. **Sentinel site monitoring**

Sentinel site monitoring involves following the quality of medicines in a particular locality through time. There are no standard guidelines for selecting sites based on rural or urban location, private or public ownership, and sampling methods (e.g., 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.

5.4. Sampling plans

Sampling plans should be prepared for each area/geopolitical zone involved in the survey and should follow the requirements of the Survey protocol and must include:

- Individual sites where sample collectors should collect samples (by facility type and address, possibly including global positioning system (GPS) coordinates)
- Medicines to be sampled (by APIs, dosage form, strength, and, if needed, also package size)
- Minimum number of dosage units to be collected per sample
- Number of samples to be collected per medicine
- Total number of samples to be collected in the relevant area/states/zones (this number may be determined using an appropriate sample size calculator such as the Cochran formula).
- All products that are to be sampled and the rationale for selecting the products
- Timeframe for sampling
- Defined, determined, and approved budget
- Include and inform laboratories involved for planning purposes
- SOPs to address sampling plans
- Detailed instructions for sample collectors.

5.4.1. Number of dosage units to be collected

The number of dosage units that should be collected per sample depends on the Survey objectives, medicines selected for surveillance, tests to be conducted, testing methods to be employed, and available resources. To protect the 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 collected per sample. In relation to the available package sizes, 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 (where possible):

- Conducting the planned tests.
- Investigation and confirmatory testing for those found to be out-of-specification (OOS);
- 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 Survey protocol and in accordance with the NAFDAC sampling guide. A minimum sample size needed for any prescribed test as specified in the protocol may also be corrected when the prescribed sample size is not feasible. When a further investigation of the product quality is warranted, the NAFDAC investigation procedure should be followed. The advantage of surveillance studies using pharmacopeial/ compendial procedures is the ability to apply quality acceptance criteria as defined in pharmacopeias. The disadvantage is rather time- and resource-demanding laboratory testing leading to lower numbers of samples that can be included in the Survey.

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, or a larger number of samples can be collected through the mystery-shopper approach 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.

NAFDAC sample collectors should use sampling procedures that guarantee the collection of representative samples.

5.5. Sample collection

The TWG will be responsible for training sample collectors to be familiar with the project, Survey protocol, sampling plan, and instructions for collection of samples. Staff from NAFDAC and the different public health programs may provide useful insight into the surveillance Survey planning.

The sample collectors should have a clear understanding of the data collection instructions and procedures.

The following principles should be included in detailed instructions for sample collectors:

- Sample collectors should understand the written training procedures and should adhere to them.
- 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.
- The target medicines, their dosage forms, strengths, and 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 must be made. It should be taken into consideration that mystery shoppers requesting a very specific brand of product may alert sellers. However, such an approach may be required if evidence suggests that only one brand of essential medicine is afflicted by falsification or substandard production. It may be useful to consider using a specific written prescription for several items including the target medicine. This can reduce suspicion of a verbal request. Using the written prescription format may also enable Surveying the quality of dispensing, labelling directions, and counseling
- All units of one sample must be of the same batch number
- The medicine samples should not be removed from their original primary and secondary packaging, although they can be taken out of larger secondary packs. Packaging such as bottles and vials should not be opened. In cases where medicines are sold without package leaflets, in unlabeled plastic bags coming out of large-sized boxes (locally repacked), or as individual dosage forms, this should be recorded.
- Samples collected should have at least six months to expiry to allow sufficient time for chemical analysis except for products with not more than six months of shelf life. However, the frequency of expired medicines is also an important outcome and any expired medicine found in the outlet should be recorded
- The medicine labels and package leaflets should not be removed or damaged
- Each sample should be recorded separately using the sample collection form (see 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
- 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, for example, blisters should be 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

- 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
- Storage conditions at the site (temperature, humidity, access to light, and any other observation) should be described in the sample collection form. When overt sampling is used, sample collectors can measure temperature if not controlled on the site. Mystery shoppers can estimate and record the temperature
- 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, within which samples should be collected and the deadline for sending the last sample to the testing laboratory, should be indicated in the procedures and followed.

Normally samples of collected medicines should be paid for by sample–collectors. The exception to this is the cases where there is approved written permission to take samples from any facility without payment. The cost of collected samples must be considered when determining the number of samples to be collected.

Sample collectors should be mindful of the stock of sampled products in outlets, and potential difficulties for replacement 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 Survey, or, less desirably, collection of that particular product in that outlet should be omitted.

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

5.6.1. **Overt sampling versus mystery-shopper approach**

The decision on who should collect samples will depend on the Survey objectives, the 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 Survey 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 should be performed by someone not living directly in the same wider community. 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 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, and 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 Survey objectives. Collected samples

should be properly identified and stored, e.g. in a plastic bag labelled with the product's name and the outlet of purchase.

Upon returning from each outlet, the mystery shopper should brief the team leader for the surveillance area. 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. Other team members should double-check the original text with translation for accuracy and keep it.

5.6.2. Instructions to Sample Collectors

The Technical Working Group (TWG) will arrange to train sample collectors to familiarize them with the project, survey protocol, sampling plan, and instructions for collecting samples in line with ICH Q10 (Pharmaceutical Quality System).

The TWG shall provide useful insights into the survey planning. Sample collectors should understand instructions and procedures for data collection, be pilot-tested, and revise if necessary. The following principles should be stated as detailed instructions for Sample collectors.

- 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.
- The target medicines, dosage forms, strengths, and 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 which to choose if a selection has to be made. It should be taken into consideration that when Mystery shoppers are 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 essential medicine is affected by falsification or substandard production. It may be useful to consider using a specific written prescription for several items including the target medicine. This can reduce the suspicion raised by a verbal request. Using the written prescription format may also enable the quality of dispensing, labeling directions, and counseling to be studied.
- All units of one sample should have the same batch number. The medicine samples should not be taken out of the original primary and secondary packaging

(although removal from large secondary packs is appropriate). Containers such as bottles and vials should not be opened. Where medicines are sold without package leaflets, or in unlabeled plastic bags coming from large-sized boxes (locally repacked), or as individual dosage forms, should be recorded.

- Ideally, samples collected should have at least six months before expiry to allow sufficient time for chemical analysis. However, the frequency of expired medicines is also important outcome measure and any expired medicine found in the outlet should be recorded.
- The medicine labels and package leaflets should not be removed or damaged.
- Each sample should be recorded separately using the sample collection form (for example see Appendix 1). Whenever the required information is not available this should be noted in the appropriate space on the sample collection form; any observed abnormalities should also be recorded.
- 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. It should be written legibly and should not obscure 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 an envelope marked with the appropriate sample code and product trade name). For large surveys, barcode systems may be helpful to reduce errors.
- Where applicable, if overt sampling is used, the manufacturer's batch certificates of analysis should be collected with the samples, if available, and kept with the sample collection form.
- Storage conditions at the site (temperature, humidity, access to light, and any other observations) should be described in the sample collection form. When overt sampling is used collectors can measure the temperature if it is not controlled at the site. Mystery shoppers can estimate and record the temperature.
- Samples should be collected and kept under controlled conditions indicated on 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 taken; medicine boxes should be kept under lock.

  The period within which samples should be collected and the deadline for sending the last sample to the testing laboratory should be indicated and adhered

to. Normally samples of collected medicines should be paid for by collectors. The cost of samples should be considered when determining the number of samples to be collected. Sample collectors should be mindful of the stock of sampled products held in outlets and of the potential difficulties of replenishing sampled medicines through the supply chain, so as not to jeopardize the availability of these medicines to patients. Suppose there is a risk of product shortage after sampling. In that case, replacement of the sampled amount should be arranged immediately after the survey or, less desirably, collection of that particular product from that outlet should be omitted.

For surveys seeking to determine the proportion of poor-quality medicines sold to patients, data on product-specific sales volumes from the outlets may be necessary. These data can be collected after sampling, especially when the mystery-shopper approach is used, and sellers should be informed about the survey. This approach requires the support of the Agency as data on sales volumes can be collected by NAFDAC officers.

5.6. Storage and transportation of samples

Storage and transportation of the samples to the testing laboratory should be done according to the procedures stated in the

National Quality Assurance Policy book (NAQAP 2015 and NAFDAC GDP 2016), and according to Good Storage Practice and Good Distribution Practice guidelines. Handling of samples should be done as quickly as possible so as not to jeopardize the quality of the samples collected.

a) The storage and handling conditions of samples should comply with all national regulatory procedures.
b) The storage condition of the samples must comply with the recommendations of the manufacturer.
c) Storage areas should be clean and free from accumulated waste and vermin. Sample collectors must ensure that premises and storage areas are cleaned regularly.
d) There should 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.
e) There should be appropriate procedures for the clean-up of any spillage to ensure complete removal of any risk of contamination of samples.

f) Receiving and dispatch bays should protect pharmaceutical products from adverse weather conditions. Receiving areas should be designed and equipped to allow incoming samples to be cleaned if necessary before storage. (NAFDAC GDP 2016)

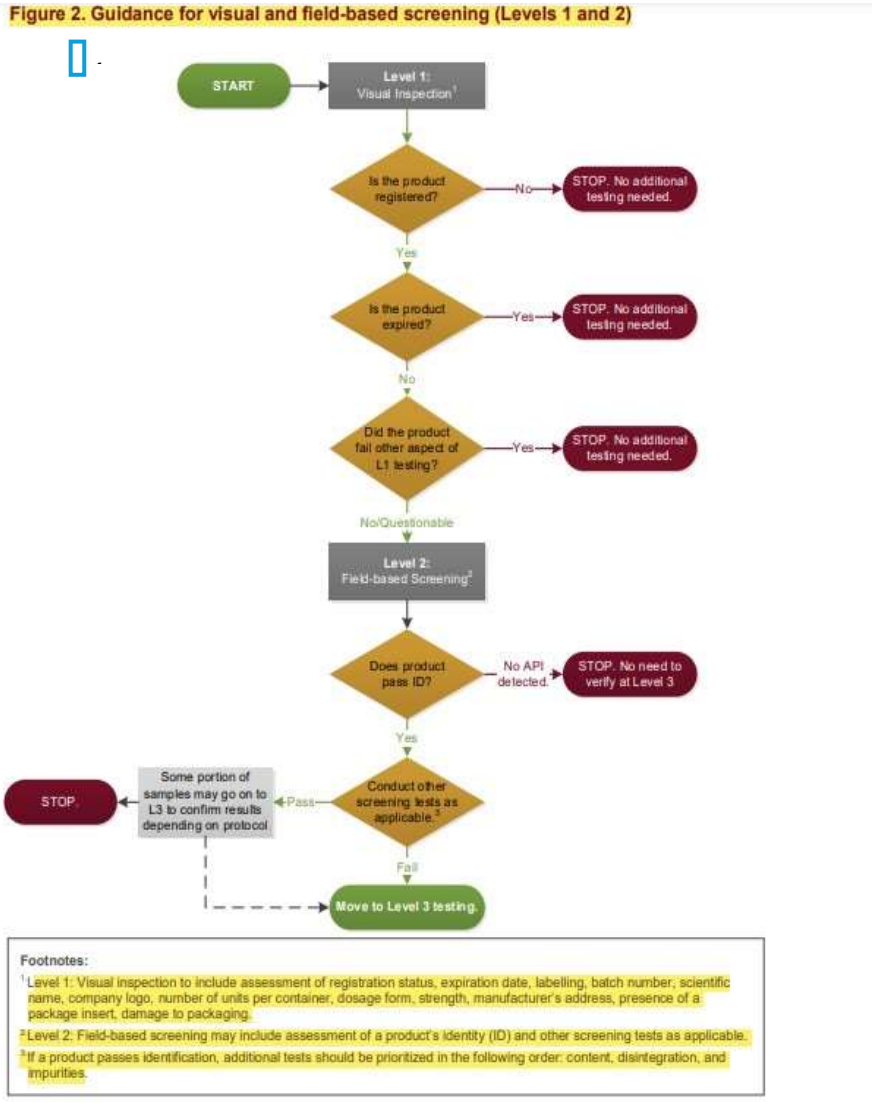
g) Medicines and other health product samples should be stored separately from other products likely to alter them and should be protected from the harmful effects of light, temperature, moisture, and other external factors.

h) 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. (NQAP 2015

- 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.
- 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.
- In case of temperature-sensitive medicines, temperature data loggers may be included within shipments to document adequate temperature in prolonged transit.
- A cover letter, copies of sample collection forms and, if available, copies of the manufacturer's batch certificate of analysis should accompany the samples.
- In the case that sample collectors are not transporting samples directly to the testing laboratory, samples with the accompanying documents should be sent by 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 the manufacturer's batch certificates of analysis should also be sent to the survey coordinator or person preparing the survey report.

5.7. Testing

Flow chart for medicine product testing:



5.7.1. Testing laboratory

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

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

- The laboratory is capable of performing tests required by the testing protocol
- The laboratory has sufficient capacity and agrees to test the required 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 could be more laboratories to use in testing of the samples collected in the study and this may depend on the number of samples.

If more than one laboratory is involved in testing the collected samples, the samples should be divided among the 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 specified in addition to the usual elements of such agreements (such as test parameters, deadlines, financial arrangements, etc.):

- 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
- Responsibilities of the laboratory during the study as specified in the protocol.
- Confidentiality declaration of the laboratory
- 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 the medicines assigned for testing to the 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 laboratory for testing.

5.7.2. 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 in line with ICH Q7 (Good Manufacturing Practice) and ICH Q2 (Validation of Analytical Procedures). Depending on the study objectives, target medicines, and available resources, the tests to be applied to samples collected in the study may include:

- Verifying the identity.
- Performing complete pharmacopeial or analogous testing.
- 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:

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

The inclusion of uniformity of content for single-dose dosage forms, or sterility and bacterial endotoxin tests, which are costly, time-consuming, and need more dosage units to be collected, should be considered with target medicines and available resources. It is impossible to achieve 100% certainty about the 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.

The packaging of each collected sample, labeling, and package leaflets should be inspected visually for any signs of substandard and falsified (SF) medical products.

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

screening methods do not provide a full picture of the quality of medicines and may underestimate non-compliant findings, compared 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.

5.7.3. 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 Nigeria but it indicates the need to look at the product and conditions of regulatory approval more closely and further actions should be considered by NAFDAC.

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. Despite efforts to harmonize pharmacopeias, there are still many differences. When a monograph for a 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 pharmacopeias or the existing monographs do not provide for desired tests, a validated method of the laboratory should be used.

5.7.4. **Receipt and testing of samples by a testing laboratory**

When samples are received, the testing laboratory should:

- Inspect each sample to ensure that the labeling 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.
- Conduct quality testing in line with the testing protocol and 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 the investigation report.
- 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);
- 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.

6.0. Data management and publication

To allow proper interpretation of data obtained during the 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 by taking suitable precautions. For analysis of large sets of data statistical software may be used. If relevant, the personal identification of individuals who participated in the study (buyers, sellers, etc.) should be entered into the database using codes only.

NAFDAC 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 testing methods would be in compliance with the compendial specification. Once the study results are compiled, evaluated, and summarized, it is recommended that NAFDAC 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 medicine quality studies can also be found in published literature.

- The report should be publicized as widely and openly as possible on the NAFDAC websites and via its social media handles in line with *ICH E3 (Clinical Study Reports)*. The results should provide feedback on the effectiveness of the QA system and influence national policies as well as have a direct impact on individuals and public health.

References

1. National Quality Assurance Policy (NQAP) 2015
2. Guidelines on Quality Control Testing of Antimalarial Medicines at NAFDAC ISO 17025 Accredited Laboratories
3. NAFDAC Good Distribution Practice (GDP 2016)
4. Medicines Risk-Based Surveillance Tool (MedRS Tool) Available at https://medrsv2.com/

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Appendix 1 Example of a sample collection form (Form Reviewed)
Appendix 2 Content of the analytical test report/certificate of analysis (Reviewed)

NAFDAC Risk-Based Sampling of Regulated Products
PMS Data Collection Form (Forms will Be Electronic)

Part A - Data from the Sampling Site and Product Label

State: ……
Sample code: ……
(State code/medicine abbreviation/sequence number/sampling date e.g., ddmmyy)

NB: If the Expiry Date on the Product is Less than six (6) Months, DO NOT SAMPLE, if More than six (6) Months, Continue.

1. Name of the facility where the sample was taken: ……
2. Address of facility:……..
3. Town/City of Facility ……..
4. Type of facility: ……
5. GPS Coordinates: Longitude ……. …. Latitude ……..
6. Method of sample collection: Overt ☐ Covert ☐
7. Product Trade name of the sample (if applicable): ……
8. Name of active pharmaceutical ingredient(s) (INN) and strength:……
   ……
9. Dosage form: ……
10. Package size, type, and packaging material of the container:
    ……..
11. Batch/lot number: ……
    Date of manufacture:(DD/MM/YYYY): ……

Expiry date: (DD/MM/YYYY): ……..
12. NAFDAC Reg. No: ……..
13. Name of the market authorisation holder: ……..
14. Address of Market Authorization Holder ……..
15. Name of Manufacturer ……..
16. Address of the manufacturer: ……
17. City of Manufacturer ……..
18. Country of Manufacturer ……..
19. Quantity collected (number of dosage units i.e. tablets/capsules etc. and number of packages): ……
20. Product information – label, information leaflet (Patient and Professional) included:
    Yes: ☐ No ☐
21. Storage conditions at the sampling site at the time of collection:
    ……
22. Abnormalities, remarks, observations: (including whether suspected SF, were more than 1 brand offered etc):
    ……
    ……
    ……
23. Date Sample Was Collected ……..
24. Name of Facility representative ……
25. Designation Facility representative ……..
26. Any other information:……
27. Name of Sample Collector ……..
28. Signature of Sample Collector ……..

Part B – Data from Tested Samples in the Laboratory

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

i. Name and address of the laboratory performing the sample testing
ii. Name and address of the originator of the request for testing
iii. Number/code of the analytical test report/certificate of analysis
iv. 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)
v. Date on which the sample was received
vi. Name of the area, region or country where the sample was collected
vii. Sample product name (trade name as it appears on the label), 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)
viii. Description of the sample (describing both the product and the primary and secondary packaging, type and packaging material of primary container); if there is any sign of unsatisfactory handling during transportation, this should be mentioned
ix. Batch number of the sample, expiry date and, if available, date of manufacture
x. Number of units received for the sample
xi. Name and full address of the manufacturer (as specified on the label or in the package leaflet)
xii. Reference to the specifications used for testing the sample, including the limits
xiii. If a reference substance was used for quantitative determination, this substance should be specified (e.g. The International Pharmacopoeia, British Pharmacopoeia or United States Pharmacopeia reference substance or working standard)
xiv. 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:
   - for content uniformity, all results for individual units,
   - for dissolution test, results for all tablets tested,
   - for assay, results of each individual sample preparation (usually 3 sample preparations), the average and the relative standard deviation; in the case of an OOS result followed by re-testing, also the investigation report and results of re-testing

- Conclusion as to whether or not the sample complies with the specifications set for the survey.
- Date on which the test was completed.
- Signature of the head of the laboratory or authorized person.