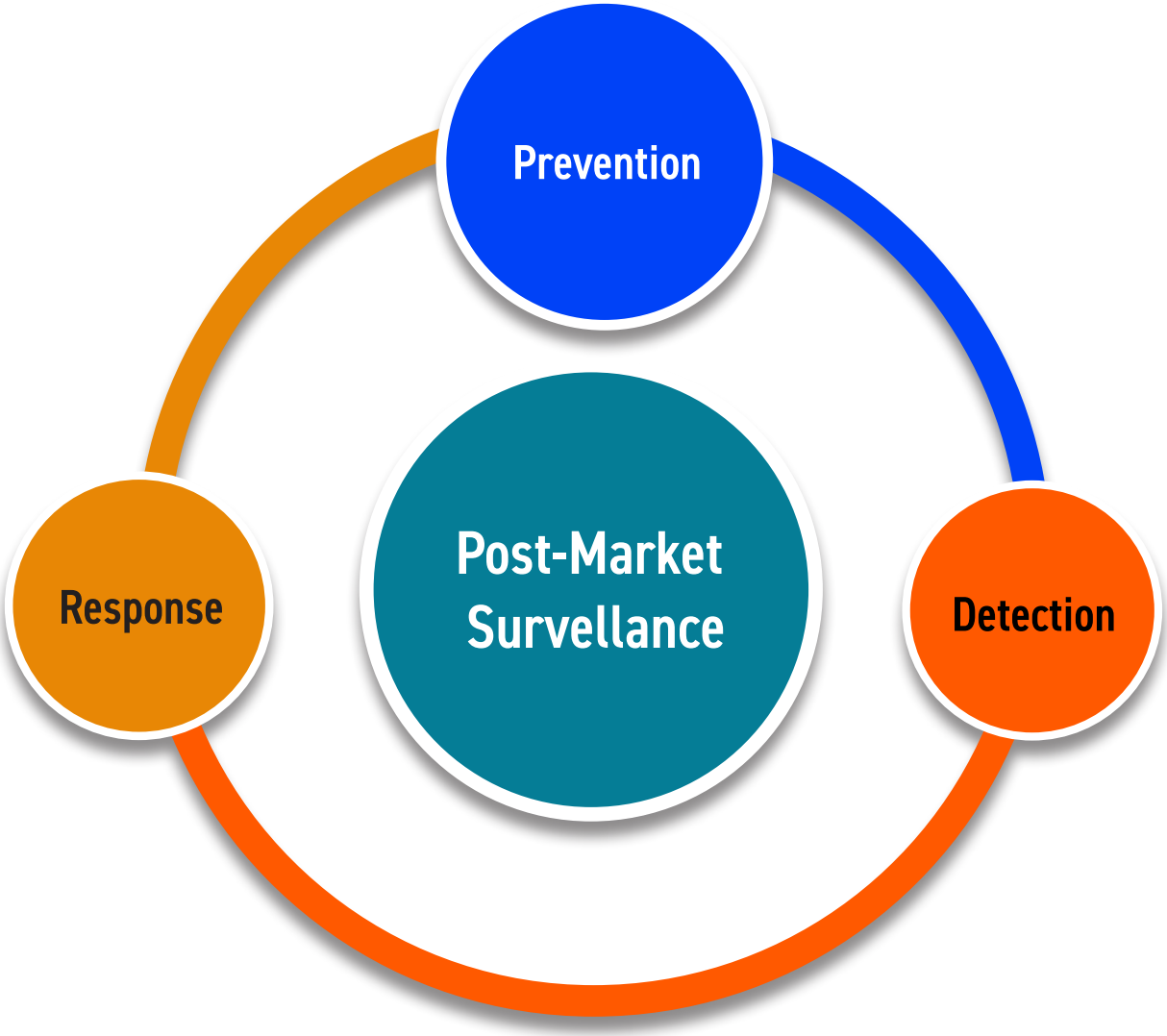
REPUBLIC OF KENYA

MINISTRY OF HEALTH



POST-MARKET SURVEILLANCE FOR IN_VITRO DIAGNOSTICS IN KENYA

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FOREWORD

The World Health Organization (WHO) Global Model Regulatory Framework for Medical Devices, including In-Vitro Diagnostic Medical Devices (IVDs) guides countries to develop and implement regulatory controls relating to medical devices to ensure their quality and safety. This requires the implementation of post-market surveillance (PMS) systems where users, patients, and manufacturers of medical devices, through the authorized National Regulatory Body which is Pharmacy and Poisons Board, can report complaints involving medical devices, including a malfunction at the device level and adverse events at the patient level. This implementation guide provides a framework, for receiving and evaluating feedback for post-market surveillance in Kenya. This guide also lists the activities of the Pharmacy and Poisons Board to act upon receipt of complaints and reports of adverse events, so-called vigilance. As part of the vigilance process, the manufacturer reports adverse events to the NRB and keeps the NRB updated on the actions taken concerning the adverse event. The NRB oversees the process of investigation and actions taken by manufacturers. PMS comprises activities undertaken to obtain oversight of IVDs on the market and to ensure that the safety, quality, and performance of these devices on the market are adequate.

Recent International Organization for Standardization (ISO) standards for medical devices place increased emphasis on the importance of post-market surveillance. The ISO 13485 on Quality Management Systems for medical devices, used by most manufacturers, requires a PMS system to be in place. The ISO standard on Risk Management, ISO 14971, also emphasizes PMS of IVDs. Additionally, a specific ISO guidance document on PMS for manufacturers of medical devices (ISO TR 20416) has been published. Together, these documents provide a framework for conducting PMS of IVDs and using PMS data to ensure IVDs' continued safety and performance.

The goal of this guideline is to facilitate the setting of appropriate standards for PMS of IVDs in Kenya and to provide best-practice guidelines for assessing their performance and operational characteristics. It describes the measures that should be taken to ensure the requirements for safety, quality, and performance of diagnostic IVDs are adhered to after they are placed on the market.

Dr Patrick Amoth

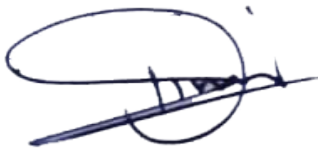
Ag. Director General, Ministry of Health

EXECUTIVE SUMMARY

In Kenya, post-market surveillance (PMS) for in-vitro diagnostics (IVDs) has mainly centered on ensuring their quality and performance by Pharmacy and Poisons Board (PPB) before distribution in the country. Downstream monitoring of IVDs following entry into the market has not been optimally implemented, The Ministry of Health is actively engaged in efforts to strengthen the national PMS system, to develop a life-cycle approach to product monitoring that integrates pre-market and post-market surveillance evaluations.

Various factors adversely affect the test performance of IVDs, compromising the quality of results obtained. These include inadequate manufacturer instructions, suboptimal shipping conditions, unsatisfactory storage conditions of IVDS, as well as the incompetence of personnel performing the test.

A proper risk mitigation system is therefore required through PMS. This entails proactive verification of new IVDS consignments and lots at the central supply stores to ensure facilities access safe, appropriate, and quality IVDS, as well as a reactive approach post-distribution, prompted by complaints from testing sites of IVDS-related product problems or malfunctions. IVD samples collected from such surveillances are subjected to analysis at identified national reference laboratories and the results are used to institute possible corrective actions. The findings of the PMS will be used to provide independent technical information on safety, quality, and performance of IVDS.



Dr Francis Kuria

Director, Directorate Of Public Health

ACKNOWLEDGEMENT

The Ministry of Health, through the Department of Laboratory Services sincerely acknowledges the contribution and hard work of the many individuals and organizations that played a role in the development of this guideline.

The development of this implementation guideline for Post Market Surveillance for In-vitro Diagnostic kits in Kenya involved an elaborate consultative process with several key stakeholders in the health sector including; National Public Health Laboratory (NHPL); Diagnostics and Clinical Support (DCS); National AIDS & STI Control Program (NASCOP); National Malaria Program (NMP); National Tuberculosis, Leprosy and Lung Disease Program; Kenya Medical Research Institute (KEMRI), Kenya Medical Supplies Authority (KEMSA); Kenya Medical Laboratory Technicians and Technologist Board (KMLTTB); Pharmacy and Poisons Board (PPB); and the County Governments.

We also want to acknowledge the invaluable support of our donors including the Centers for Disease Control and Prevention (CDC) Kenya, AMREF Health Africa, and the University of Maryland, Baltimore. Their financial and technical support played a key role in ensuring that the development of this crucial guideline came to fruition.

It is our sincere hope that the implementation of the guideline will be useful in improving the quality and regulation of IVDS in Kenya

Dr John Kiiru

Head, Department Of Laboratory Services Contents

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ACRONYMS

CAPA	Corrective Action and Preventive action
CDC	Centers for Disease Control and Prevention
DLS	Department of Laboratory Services
DNMP	Division of National Malaria Program
DNTLDP	Division of National Tuberculosis, Leprosy, and Lung Disease Program
EQAS	External quality assessment schemes
GOK	Government of Kenya
HIV,	Human Immunodeficiency Virus
INN	International Non-Proprietary Name
ISO	International Organization for Standardization
IVDS	In-vitro Diagnostics
KEMRI	Kenya Medical Research Institute
KEMSA	Kenya Medical Supplies Authority
KMLTTB	Kenya Medical Laboratory Technicians and Technologists Board
LMIS	Laboratory Management Information System
M&E	Monitoring and Evaluation
MOH	Ministry of Health
MS	Market Surveillance
NASCOP	National AIDS and STIs Control Program
NPHL	National Public Health Laboratory
NQA	Standards and Quality Assurance unit
NRB	National Regulatory Body
NRL	National Reference Laboratory
PMS	Post-market surveillance
POCT	Point of Care Testing
PPB	Pharmacy and Poisons Board
PT	Proficiency testing
QA	Quality Assurance
QC	Quality control
QMS	Quality Management Systems
rPMS	Reactive Post Market Surveillance
SDP	Service Delivery Point
TAC	Technical Advisory Committee
TAT	Turnaround Time

ToR	Terms of Reference
TWG	Technical working group
WHO	World Health Organization

GLOSSARY OF TERMS

Adverse Event: Defined as serious deterioration in the state of health of the patient or user due to product defect i.e. malfunctioning or failure, deterioration in characteristics or performance, or inadequacy of labeling or of instructions for use that directly or indirectly might lead to or might have led to the incident.

Analytical sensitivity: This is the ability of a test to detect a low concentration of a given substance. Sometimes used interchangeably as the limit of detection or detection limit

Complaint- Any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a device after it is released for distribution.

Corrective action - Action to eliminate the cause of a detected nonconformity or other undesirable situation and to prevent a recurrence.

End user: The person who uses a particular product

In-vitro diagnosis (IVDs) - A medical device, whether used alone or in combination, intended by the manufacturer for the in vitro examination of specimens derived from the human body solely or principally to provide information for diagnostic, monitoring or compatibility purposes.

Lot - a batch of finished products or goods produced, harvested, or collected together into a single group with uniform properties and has been produced in one process or series of processes.

Manufacturers: Any natural or legal person with responsibility for the design and/or manufacture of a medical device to make them, under their name; whether or not such a medical device is designed and/or manufactured by that person, themselves or on their behalf by another person(s).

National Level: Refers to the highest level as per organogram or chain of command

National Reference Laboratory - A national testing laboratory through appointment by a competent organization (ISO certification) and provides reference values in a specific technical field.

National Regulatory Body: Is an organization enacted by an Act of parliament to establish and regulate national standards for qualifications of in-vitro diagnostics and to ensure consistent compliance with them.

Post Market surveillance is a collection of processes and activities used to monitor the performance of medical devices after they have been approved and released into the market.

Post-distribution- Collecting information on the quality, safety, and/or performance of IVDS on the market after the product is distributed to the end-user.

Pre-distribution: Collecting information on quality, safety, and/or performance through verification before the product is distributed from the central warehouse to the end-user.

Preventive action - Action to eliminate the cause of a potential nonconformity or other undesirable situation and to prevent an occurrence.

Product: Refers to In-vitro diagnostics

Sample - One or more units of product, either components or finished devices, drawn from a lot without regard to the quality of the units.

Sampling: Taking a proportion of an item from the larger population for measurement.

Verification: the process of establishing the truth, accuracy or validity of something.

1. BACKGROUND

1.1. INTRODUCTION

In-vitro diagnostics (IVDS) are medical devices and accessories used to perform tests on samples taken from the human body such as blood and urine to detect the presence or absence of infection and to diagnose a medical condition and/or monitor disease. To be useful, diagnostic methods must be accurate, and simple and should also provide results in time to institute effective case management and control measures. For this reason, diagnostic testing for all diseases is becoming the mainstay of clinical medicine and public health.

Current technological developments have given rise to a plethora of IVDS that holds promise for the improved management and control of diseases. Given the increasing demand for these tests, their usefulness and utility should be evaluated in the appropriate laboratory, clinical, and/or field settings. Many variables can influence the performance of IVDS in different settings. These include differences in the characteristics of the population or infectious agent, the test methodology, whether the test is manual or automatic, the physical format of the test, and local diagnostic practice and skills. Test evaluations and verification of IVDS should therefore be performed under the range of conditions in which they are likely to be used in practice. Upon successful evaluation and approval for use in a country, continued surveillance of consistency in the performance of such IVDS is the next level of engagement in what is referred to as Post Market Surveillance (PMS).

1.2. POST-MARKET SURVEILLANCE

Post-market surveillance is a collection of processes and activities used to monitor the performance of medical devices after they have been approved and released into the market. The purpose of PMS for IVDS is to promote and facilitate access to safe, appropriate and affordable IVDS of good quality equitably. Malfunctions of IVDS may cause adverse events, such as serious injuries, deaths, and associated product challenges. Therefore, the findings of PMS are used to provide independent technical information on the safety, quality, and performance of IVDS.

The need for PMS arises immediately upon the commercialization of the device. In the context of the WHO Pre-qualification of In-Vitro Diagnostics Programme, manufacturers of IVDS are obliged to report regularly post-market information to the Pharmacy and Poisons Board (PPB) and WHO. In Kenya, PMS for IVDS is required after their initial verification. Despite this requirement, there have been ongoing concerns about whether the current system is optimally structured to collect sufficient information for post-market surveillance of IVDS.

The Ministry of Health is actively engaged in efforts to strengthen the national PMS system for IVDS, to develop a life-cycle approach to product evaluation that integrates pre-market and post-market evaluations. At the same time, the ministry is establishing implementation systems as well as structures for the effective management of PMS.

The goal of this document is to;

- *To facilitate the setting of appropriate standards for PMS in Kenya for IVDS.*
- *To provide best-practice guidelines for assessing the performance and operational characteristics of IVDS post-market.*
- *To assist those designing IVDS post-market evaluations at all levels, from program and county to end-users,*
- *To facilitate a critical review of PMS M&E data related to IVDs*
- *To select or approve tests that have been appropriately evaluated and met defined performance targets.*

1.3. SCOPE

This guideline outlines the objectives and processes of the post-market surveillance for IVDS. It describes the measures that should be taken to ensure the ongoing requirements for safety, quality, and performance after they are placed on the market.

The intended audience of this guidance are;

- *End-users of IVDS in laboratories and other testing sites,*
- *Programme implementers,*
- *Procurement agencies, central medical stores,*
- *Staff responsible for post-market surveillance (national regulatory bodies, national reference laboratories)*
- *Manufacturers*

1.4. BASIC PRINCIPLES OF PMS

PMS is conducted to ensure performance monitoring, usability design, product quality maintenance, and to evaluate expanded indications, especially at the point of care.

Factors affecting the quality of IVDS include:

- *Personnel: Test performance can be linked directly or indirectly to the person performing the test. Personnel competence can therefore adversely affect the quality of results, attributable to the performance of procedures and/or reporting. The following should be considered during PMS;*
    - *Adequate training/continuing professional development*
    - *Quality Assurance systems in place*
    - *Good record keeping (standardized logbooks, LMIS)*
    - *Ongoing M&E*
    - *Appropriate testing algorithm*
- *Storage of commodities: In PMS, proper storage of IVDS including the temperature of the storage per the manufacturer's instructions are important aspects, which if compromised, may affect their performance.*
- *Manufacturer: New IVDS are continuously being manufactured due to changes in technology and hence quality and consistency are not always optimal. Inadequate manufacturer instructions could lead to errors in test performance or result interpretations which can affect the patients or third parties.*
- *Shipment: Transportation of IVDS from manufacturer to the country and from the central stores to end users may expose the product to varied environmental conditions. These may affect the quality of performance, hence it's important to carry a post-market survey.*

1.5. THE RATIONALE FOR POST-MARKET SURVEILLANCE

There is a need to strengthen the regulatory oversight for IVDS in Kenya for both pre-market assessment and post-market activities. This may accentuate the shortcomings in assuring safety, quality, and performance.

1.6. PRE-MARKET ASSESSMENT

Pre-market assessment of IVDS is highly recommended for any product before entry into the marketplace in each country of intended use. While premarket assessment of IVDS can provide information on a product's safety, quality, and performance, there might be questions that cannot be answered in the premarket stage or an issue may arise after the product is marketed. Hence the need to conduct PMS.

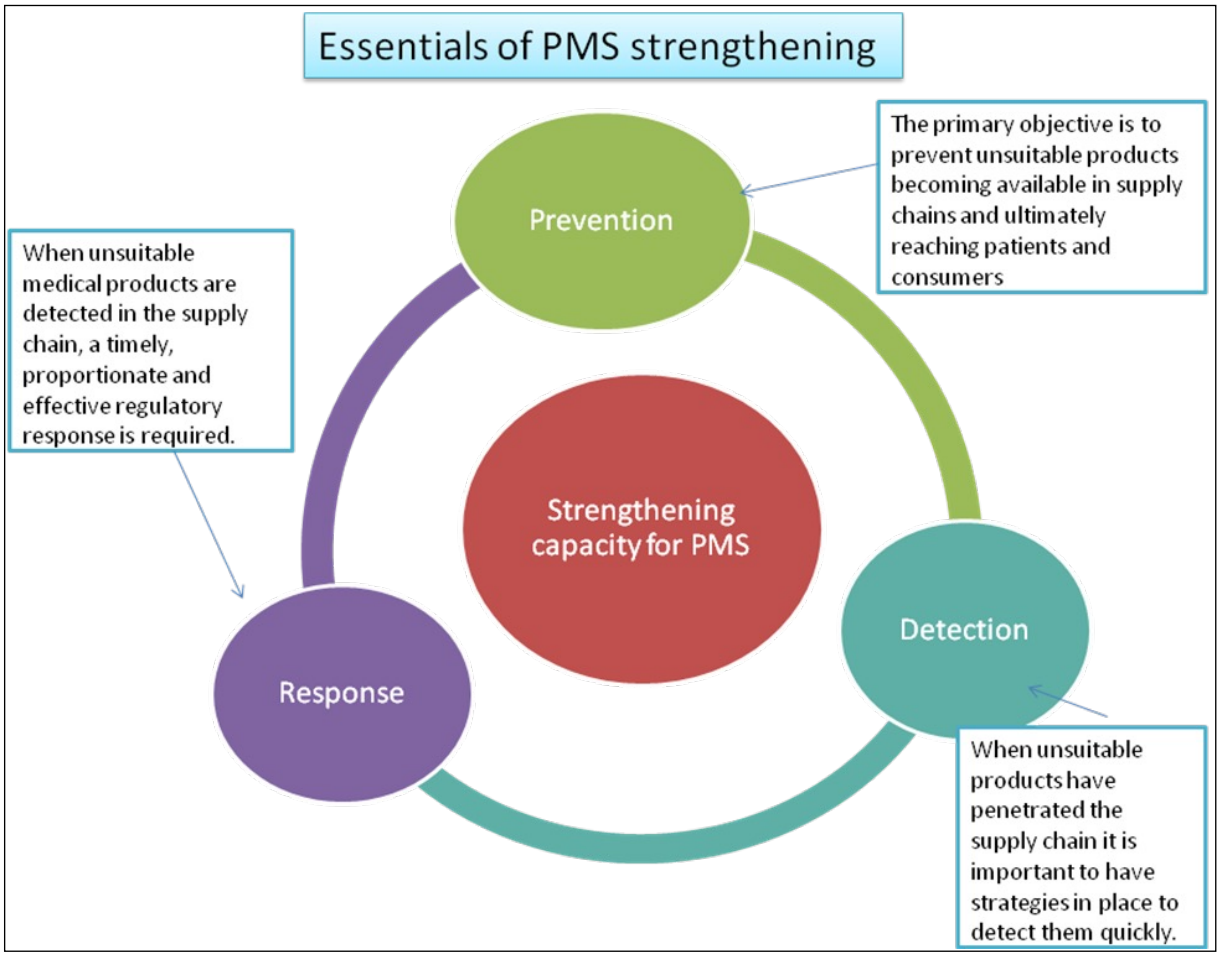
1.7. POST-MARKET SURVEILLANCE

1.7.1.OBJECTIVES OF POST-MARKET SURVEILLANCE

- *Prevention and Detection of adverse events (injury, harm or death)*
- *Development of quality standards*
- *Regulatory refinement*
- *Product improvement*
- *Corrective action*

1.7.2. FUNDAMENTALS OF POST-MARKET SURVEILLANCE

For PMS to be effective, capacities at various levels require to be strengthened. Personnel training is crucial and facilities handling PMS require structural strengthening. An oversight committee that brings together all players at the National level is a prerequisite.



2. STAKEHOLDERS IN POST-MARKET INTERVENTIONS

2.1. STAKEHOLDERS

The stakeholders play a crucial role in post-market intervention through roles and responsibilities. There are various stakeholders in the PMS and these include:

- *Technical advisory committee*
- *Pharmacy and Poisons Board (PPB)*
- *National reference Labs*
- *Manufactures/suppliers*
- *End users*

2.2. STAKEHOLDERS ROLES AND RESPONSIBILITIES

2.2.1. TECHNICAL ADVISORY COMMITTEE

The technical advisory committee (TAC) is the key stakeholder engaged to advice, facilitate, and offer assistance on any matter. The TAC is composed of representation from the following; NPHL respective departments, Donors, KEMSA, KEMRI, Counties, and Partners. The roles and responsibilities of the TAC will include;

- *Coordinate the PMS activities*
- *Resource mobilization*
- *To develop and review the PMS documents*
- *Identify recommended improvements and initiatives from other stakeholders*
- *Provide oversight in the various in PMS*
- *Provide advice on all aspects of PMS to help in decision-making. i.e. review and disseminate all the PMS reports*
- *Promote and contribute towards the development and sustainability of post-market surveillance activities.*
- *Constitute Sampling/analysis team for PMs activities*
- *Support the National Public Health Laboratory in the testing of IVDS in PMS*

2.2.2. NATIONAL REGULATORY BODIES

These comprise the regulatory bodies such as the Pharmacy and Poisons Board (PPB) involved in the regulation of the IVDS in the country. Their roles and responsibilities will include to;

- *Take regulatory action in all aspects of PMS*
- *Oversee the lot validation of the IVDS*
- *Collect and validate all post-market information and share it with other stakeholders.*
- *Designate and assign an accredited national reference laboratory to conduct lot verification testing.*

2.2.3. NATIONAL REFERENCE LABS

The National Reference Laboratories shall adhere to internationally recognized quality standards, e.g. ISO 15189 for Medical laboratories, particular requirements for quality and competence, or ISO 17025. Roles will include to;

- *Perform laboratory testing for post-market surveillance.*
- *Participate in external quality assessment schemes (EQAS), and act on results, if required.*
- *Analyze and archive PMS samples*
- *Report PMS results.*

2.2.4. END USERS/SERVICE PROVIDERS

The end-user/service provider will;

- *Give feedback on the IVD's performance in the field.*
- *Handle and use IVDS according to the manufacturer's instructions for use to maintain their quality, safety, and performance.*
- *Ensure proper storage of the test kits according to the manufacturer's instructions for use and should monitor the temperature of the storage facility.*
- *Document the complaint fully by determining all aspects and possible causes such as product quality, safety or performance, use error, and abnormal use.*
- *Notify the relevant authority of all complaints related to the use of their product.*

2.2.5. MANUFACTURER

Manufacturers of IVDS should be familiar with quality management systems requirements for regulatory purposes and standards including:

- *ISO 9001:2008 - Quality management systems Requirements,*
- *ISO 13485:2003 - Medical devices*
- *ISO 14971:2007 - Medical devices - Application of risk management, which outline their requirements for compliance with post-market surveillance aspects of these standards.*

They are expected to adhere to available international standards such as:

- *ISO2859:2006, Sampling procedures for inspection by attributes series*
- *ISO 3951: 2013, Sampling procedures for inspection by variables series to verify the safety, quality and performance of each lot manufactured of their products.*
- *Perform quality control lot release as part of the requirements of ISO 13485:2003 Medical devices.*

Manufacturers should:

Designate a person to be in charge of PMS information exchange with the end users and national regulatory bodies

- *Maintain all types of reports related to complaints and annual post market surveillance summary reports*
- *Develop a process to identify and control a product that does not conform to the required standards and to prevent its unintended use*
- *Designate a competent person to facilitate traceability for LOTs of IVDS to end users as per their laid-out procedures.*

3. CONDUCTING POST-MARKET SURVEILLANCE FOR IVDS

3.1. POST-MARKET SURVEILLANCE STRATEGY

Post Market Surveillance is conducted by the Pharmacy and Poisons Board (PPB) within the Ministry of Health, in collaboration with various types of organizations, and agencies, including IVD Manufacturers. The purpose of conducting PMS may differ, depending on the perspective of conducting the surveillance. PMS involves systematic monitoring of products as they are used in real-life scenarios, as opposed to the controlled settings in pre-marketing trials, where study conditions are tightly controlled. PMS provides valuable information on the use of products information not easily obtainable from pre-marketing studies. After a new medical device is brought to market, the process of PMS provides an ongoing assessment of safety, risks, and effectiveness.

PMS is likely to: -

- *Identify poorly performing devices*
- *Accurately characterize and disseminate information about real-world device performance, including the clinical benefits and risks of marketed devices.*
- *Efficiently generate data to support premarket clearance or approval of new devices and new uses of currently marketed devices.*

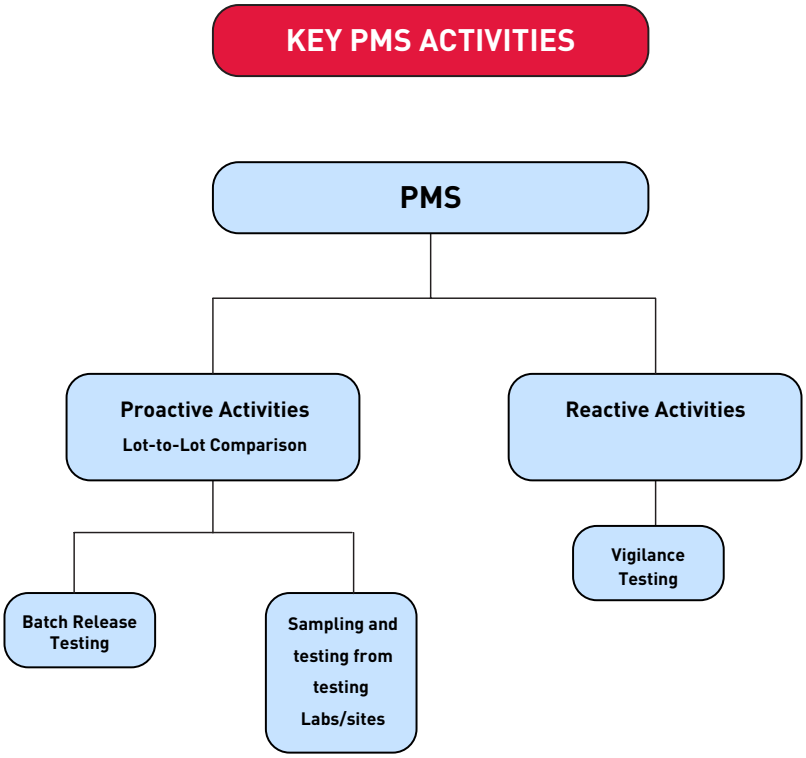
In Kenya, PMS will cover the different levels of health facilities and affiliations. Information and samples on all IVDS will be collected from the central supply stores pre-distribution by Pharmacy and Poisons Board. Post distribution information and IVDS will be collected from selected health facilities in the country, research institutions, government agencies, private companies, non-governmental organizations (NGOs), Faith-based organizations (FBOs), and consumer advocacy groups. Sufficient additional quantities of IVDS should be procured to enable the collection of post-market surveillance data.

3.2. IN-COUNTRY POST MARKET SURVEILLANCE DESIGN

The PMS program entails proactive and reactive approaches. Proactive assessment involves identifying a problem before it affects a clinical decision. Reactive assessment is initiated through complaints from end users and feedback.

Proactive PMS: Information on the quality, safety, or performance of an IVDS on the market is collected proactively through lot verification testing. This testing is conducted after shipment to the buyer (countries) and can be performed both pre-distribution and post-distribution to end-users. Manufacturers also should conduct post-market surveillance by actively gathering evidence in the literature on their product or similar products and by seeking feedback from customers.

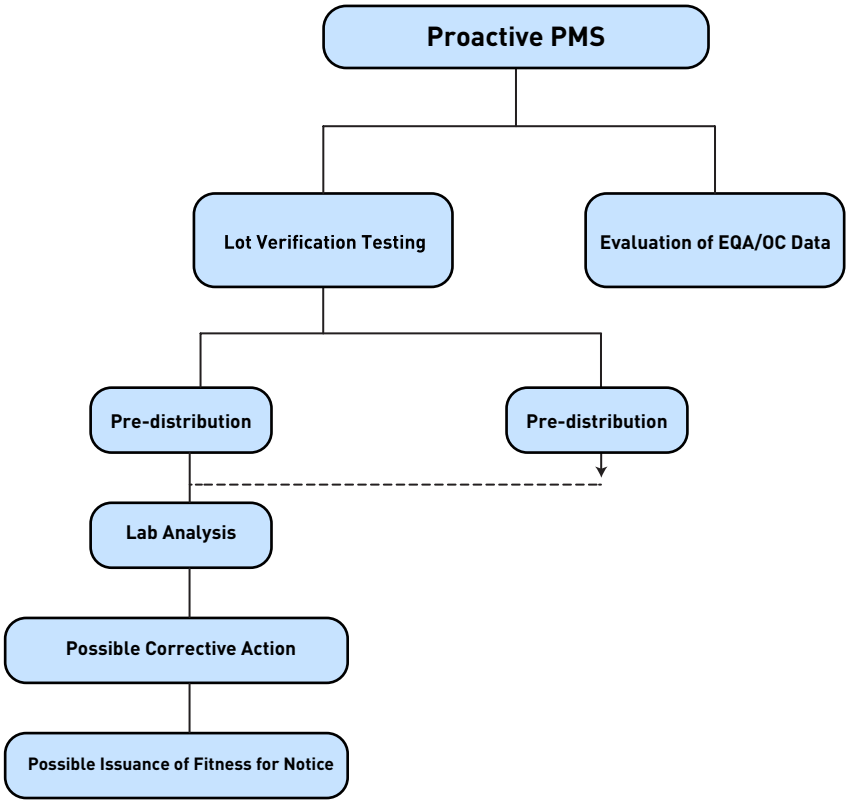
Reactive PMS: Reactive PMS is done through notification and evaluation of complaints including notification and evaluation of adverse events.



3.3. PROACTIVE POST-MARKET MECHANISM

This is a process that entails:

- *Lot verification*
- *Independent of the manufacturer*
- *Ensures that only lots meeting established criteria are used*
- *Use a risk-based approach*
- *Evaluation of EQAS and QC testing results –Across sites using the same assay, same/different lot*



3.3.1. LOT VERIFICATION

Lot verification testing of IVDS is conducted after shipment to the country and will be performed by a national reference laboratory both pre-distribution and post-distribution to end users. Lot verification aims to identify any catastrophic product failure and to determine variation from one lot to the next. This ascertains that IVDS continue to conform to their specifications and have not been adversely affected by inappropriate storage and transport conditions.

Pre-distribution

Pre-distribution lot verification is used to verify:

- *Safety, quality, and performance requirements are met when the IVDS are in use*
- *Transport and/or storage conditions have not affected the performance of the IVDS*
- *Stability (shelf life) claims made by the manufacturer are met*

Pre-distribution lot verification will be done on receipt at the central store before distribution to testing sites.

Sampling at the central store

Sampling will be done from central stores or similar centralized warehouses.according to the approved PMS protocol and sampling plans as guided by PPB. Relevant trained and competent personnel constituted by the Technical Advisory Committee (TAC) will conduct the sampling based on a pre-determined sampling criterion. Each lot will be sampled. A representative sample of tests per lot should be taken. The number of tests will depend on the protocol chosen.

On receipt of IVDS consignment, the central stores will notify the TAC that will in-turn collaborate with respective reference laboratories for verification. (The verification process shall be guided by laboratory-based protocols).

A convenient sample, depending on the determined sampling criteria of all IVDS of the new lot or consignment will be selected and submitted to the reference laboratories for analysis.

During the verification process at the laboratory, a comparison of technical and physical, specification, as described by the manufacturer, will be done. The physical specifications will involve confirming that:

- *All kits are intact on supply.*
- *The products are packed as per required specifications.*
- *All labeling and package inserts are in English.*
- *Availability of clear job aid or instructions illustrating the method of use of the product.*

Storage conditions should be indicated on the product packaging. Reagents that require a cold chain should be indicated with adequate instructions. These should be adhered to during storage and transportation. Adequate directions regarding the storage of the product after the container has been opened should appear on the label and in any accompanying leaflet.

Special markings on primary, secondary, and tertiary packaging are as follows:

- *Each primary and secondary package shall contain only one product and one batch.*
- *Primary and secondary packages should be clearly labeled with indelible ink indicating the following:*
- *International Non-Proprietary Name (INN) / generic name of active ingredient (reagent, chemical, etc.)*
- *Date of Manufacture*
- *Date of Expiry*
- *Batch/lot number*
- *Technical specifications*
- *Site of manufacture showing physical address*
- *Storage instructions*
- *A comprehensive and detailed insert with methodology in English, preferably with pictorial.*
- *Certificate of analysis*

Pre-distribution data typically reflect 'short term periods of observation or use, and may not reflect potential incidents or adverse information that would arise over longer periods of time, i.e. during the post-market phase.

Post distribution

Post distribution aims at systematic collection and analysis of information about the devices as they continue being used in the market. It provides useful information on the effectiveness as well as set objectives of the IVDS.

Despite testing of the IVDS before distribution, continuous monitoring needs to be done on the same lots to maintain the required standards. Testing of samples from the field, in combination with pre-distribution lot verification testing, guarantees monitoring of IVDS quality throughout the distribution chain.

Post-distribution verifies;

- *Safety, quality and performance requirements are met when the IVDS is in use*
- *Transport and/or storage conditions have not affected the performance of the IVDS*
- *Stability (shelf life) claims made by the manufacturer are within the shelf life claimed by the manufacturer.*

Given these considerations, a properly implemented vigilance system shall be scheduled (annually or need basis) on field sampling of IVDS ensuring every lot is sampled post distribution.

A sample of IVDS from the same lot shall be taken from laboratories/testing sites at different levels of the health system as follows:

- *All tiers of health facilities*
- *Faith-based hospitals*

- *Non-Governmental Organizations*
- *Private hospitals*
- *Stand-alone testing sites*
- *Research institutions*

Different geographical areas should be covered i.e. if IVDS are from a primary care testing level that is from a geographical area that has been sampled, the next sampling should not involve a primary care testing level from the same geographical area.

Relevant trained and qualified personnel constituted by the TAC should do the sampling at all levels. Random sampling should be done according to the chosen protocol.

IVDS will be sampled with a replacement of the same kit done by the team conducting sampling. The facility assessment will comprise a structured tool to enhance information collection on IVDS.

Good sampling practices

The batch should consist of all components of the IVDS as described by the manufacturer including kit inserts and any accompanying leaflets. The sampling team will ensure samples are transported to the National Reference Testing Laboratory in such a way that the integrity of the IVDS is not adversely affected and that the appropriate storage conditions, as specified by the manufacturer, are maintained. Temperature log monitors should be included within the transportation packing for the samples.

3.3.2. EVALUATION OF EQAS AND QC TEST RESULTS

In addition to lot verification testing and complaints, sources of data on the quality and performance of IVDS on the market include external quality assessment schemes (EQAS), also known as proficiency testing (PT), and from quality control (QC) programs.

External Quality Assessment Schemes

Data generated by EQAS can be analyzed to assess the quality and performance of IVDS Although an EQAS program monitors the competency of the personnel, processes among other indicators can provide very useful information about the performance of IVDS. EQAS data analysis may indicate not only operator-related errors (for example transcription errors), but also errors related to the IVD itself, especially if large numbers of laboratories/testing sites are using the same IVDS. The lot numbers of IVDS used to test PT panels should be recorded to make this data useful. The national reference laboratory shall coordinate proficiency testing data as an indicator in monitoring post-market surveillance of the IVDS. The report findings should be shared with TAC on every EQA round and lot performance monitored.

Quality Control (QC)

A positive QC specimen is a specimen that has reactivity that is just above the cut-off for positivity of an IVDS. Similarlty, a negative QC is a specimen that is non-reactive to the test material. All attempts should be made to acquire QC materials for sites undertaking testing.

On every consignment received at the facility level, QC checks should be performed on IVDS and performance documented before use. Troubleshooting should be done and documented for any failure noted. If unresolved, the case should be reported to the national regulatory body.

3.4. REACTIVE POST-MARKET MECHANISM (VIGILANCE SYSTEM)

3.4.1. REACTIVE POST MARKET MECHANISM

This process entails reporting administrative and technical complaints by end-users/procurers/ implementers as soon as they become aware. It covers activities undertaken after any party becomes aware of adverse events, malfunctions, results of testing, or other relevant information about an IVD placed on the market.

The goal of reactive post-market surveillance (rPMS) of diagnostic IVDS is to improve the health and safety of patients/clients, users, and others by reducing the likelihood of adverse events occurring and recurring.

The objectives of rPMS can be achieved through;

- *Evaluation of reported adverse events*
- *Dissemination of information that could provide a driving force to prevent or minimize the consequences of adverse events*
- *Modifying/ removing the IVDS from the market*
- *Data mining and M&E reports*
- *Other appropriate corrective actions instituted*

Information on the quality, safety, or performance of IVDS on the market will be collected reactively (after the problem has already occurred) following suspicion that it may have affected a clinical decision. End IVD users, service supervisors, or other stakeholders shall share observations and experiences regarding the quality, safety, and performance of IVDS in the post-market phase. In addition, rPMS may also be triggered by information obtained from ongoing external quality assessment schemes (EQAS) or operations research data.

3.5. COMPLAINT IDENTIFICATION

It's the role of service providers to actively identify issues related to the provision of testing services. Complaints/anomalies can also be detected by M&E, quality implementers, regulatory bodies, and program officers. These issues can either be administrative or technical:

Administrative: A complaint related to any aspect of the procurement contract not fulfilled. For instance: agreed delivery time not adhered to, agreed guaranteed shelf life upon delivery not adhered to, incorrect product and/or quantity and quality delivered, unauthorized, etc.

Technical: A complaint, affecting the safety, quality, and performance of the IVDS. In Kenya, some of the technical complaints experienced include:

- *Increased screening and confirmatory test result discrepancy (>2 %)*
- *Increased results invalidity (>1%)*
- *Insufficient clarity of reactivity markers*
- *Insufficiency of test reagents*
- *Presence of visible reactivity markers before device use*
- *Reaction with specimen other than the specified one or other substance (s) e.g. for blood-based reacting with urine or water.*
- *Inaccuracy in the labeling.*
- *Inappropriate instructions for use*
- *Insufficient /missing information e.g. expiry date.*

Information about such issues may become available besides reports from service providers through, for example, literature and other scientific documentation.

3.5.1. DOCUMENTATION OF COMPLAINTS

Service providers should document any problems with IVDS using information obtained from the testing service registers, inventory records, item requisition and delivery records. These may include affected product code(s), affected lot number(s), and expiry date(s), affected consignments of IVDS and any measures taken. Where possible, photographs of affected IVDS should be taken to illustrate the problem. Users should keep and appropriately store at least 1-2 affected samples of IVDS as retention kits for later testing, if required.

3.5.2 VERIFICATION OF COMPLAINT AT SERVICE DELIVERY POINT (SDP)

Verification of possible complaints will be conducted by the service provider, in association with their site supervisor. Service providers should conduct a preliminary investigation to identify complaints that are related purely to user error or abnormal use, not to the IVDS itself. These errors may be corrected at the testing site, without the need for additional intervention. A preliminary investigation and documentation step will also generate more detailed information on the circumstances related to the complaint and enable the responsible agencies to conduct a more in-depth investigation of their own.

Verification of complaints may also require the engagement of county management structures. County laboratory coordinators in conjunction with the QMS team at the county level will during the oversight role, be actively engaged in reactive PMS issues when the need arises.

3.5.3 REPORTING OF VERIFIED COMPLAINTS TO THE COUNTY LEVEL AND NATIONAL AGENCIES

In case it is difficult to determine if an adverse event was the consequence of a problem with the IVDS itself or an error by the service provider, or it is suspected that the problem is purely due to the IVDS; verified complaints should be reported to the County Medical Laboratory Coordinator then to National QA program and supplies agency with a notification to the regulatory body for appropriate intervention.

3.5.4 CONFIRMATION OF COMPLAINTS

Confirmation of complaints will be conducted by National Public Health Laboratories (NPHL) Quality Manager. At least 1-2 IVDS associated with the problem and which had been retained and kept appropriately will be sampled. The required documentation will be done using standard sampling tools. The IVDS will be transported appropriately to the National Reference Laboratory for confirmation and validation of the complaint(s).

At the laboratory, the sampled IVDS will be evaluated using the standardized operational procedures. . If results from the laboratory evaluation confirm the existence of the problem, a report will be prepared and submitted to the TAC for adoption and appropriate action instituted. However, if the laboratory evaluation results confirm otherwise, the report should be submitted to the committee and at the same time, appropriate interventions should be instituted at the site of the complaint.

In case the problem/complaint is identified from data analysis at the SDP, the following should be done:

- *Conduct QA audit at the specific area of concern at the site level*
- *If unresolved, report to the county level who will escalate to the National reference lab and then to TAC for specific follow-up actions*

In the event of testing anomalies noted from the program level, the county team can review their QMS. Corrective intervention can then be implemented followed by a review of any improvements. If the anomaly persists, a report should be prepared and seek interventions from the TAC.

TACs course of action will involve:

- *Sampling the same lots associated with the anomaly from the data, if available at the site, or from neighboring sites for confirmation*
- *Sampling from already existing kits*
- *Conducting a thorough QA audit*
- *These sampled kits should be subjected to laboratory evaluation as described in Laboratory Analysis Proactive PMS.*

If the report indicates that the set criteria failed [e.g. >1% invalidity for HIV), the TAC should be informed and a joint decision with the regulatory body on the next steps should be made. The lot in question should be isolated and quarantined until the matter is resolved and feedback is given.

For any nonconforming lot, WHO and NRB will ensure that the manufacturer undertakes a root cause analysis and conducts field safety corrective action.

4. RESPONSES IN POST-MARKET SURVEILLANCE

When unsuitable IVDS are detected in the supply chain, an effective regulatory response is required. The response is done through notification and evaluation of complaints, including notification and evaluation of adverse events.

4.1 INTERVENTIONS

4.1.1 UTILIZATION OF PMS REPORT

Reports generated from reactive PMS will determine the interventions required. Such interventions may include:

- *IVDS recall*
- *Recall of specific IVD lots*
- *QA auditing*
- *Corrective actions*
- *Report to National Regulatory Body*
- *Depending on the seriousness of the IVDS deficiency discovered in the post-market phase and/or potential for future harm, the National Regulatory Body shall consider the following possibilities as well:*
- *Perform additional in-use surveillance of the IVDS concerned.*
- *Issue an alert advising service providers*
- *Require the manufacturer to make appropriate changes in the design, manufacturing process, or information supplied with the product*
- *Send the data acquired to the manufacturer and store it in a database to help identify trends that require action.*

4.1.2 LABORATORY ANALYSIS

The TAC will coordinate the evaluation process with the testing laboratories. A national reference laboratory will be identified to perform lot verification testing. The reference laboratory should have the authority and capacity for assessing the quality, safety, and performance of IVDS.

The National reference laboratories shall:

- *Be mandated by the National regulatory body to perform laboratory testing for post-market surveillance of IVDS (both pre-distribution and post-distribution), and therefore have sufficient resources to conduct lot verification testing.*
- *Strive to adhere to internationally recognized quality standards ISO 15189:2012 Medical Laboratories-Requirements for quality and competence, ISO 17025:2017 General requirements for the competence of testing and calibration laboratories or ISO 17043:2017 Requirement for proficiency testing or any other standard*

- *Participate in external quality assessment schemes (EQAs)*

Laboratory analysis will involve the use of quality control materials of known value. Same quality control panels should be used for both pre-distribution and post-distribution lot testing. The testing should be conducted on a standardized lot verification panel. The National reference laboratories should present testing results in the form of a lot testing report to TAC. The validating laboratories shall conduct testing on samples provided and issue a certificate of analysis report to the TAC within laboratory TAT.

4.1.3 OUTCOME / CORRECTIVE ACTION

Depending on the seriousness of the IVDS deficiency discovered in the post-market phase and/or potential for future harm at pre-distribution, the TAC should consider the following possibilities:

- *No action.*
- *Perform additional in-use surveillance of the IVDS concerned*
- *Issue an alert advising the central supply agency*
- *Mandate warehouse corrective action (for example quarantine)*
- *Send the data acquired to the manufacturer and store it in a database to help identify trends that require action.*

5. MONITORING AND EVALUATION

A functional national M&E system provides essential data for monitoring the implementation of programs and presenting opportunities for improving the processes. M&E data are, therefore, vital for guiding the planning, coordination, and implementation of the program as well as assessing the effectiveness and identifying areas for improvement or interventions.

5.1. DATA COLLECTION METHODS AND TECHNIQUES

Data shall be collected based on the pre-defined indicators using the standard tools. A combination of techniques shall be used such as:

- *Desk review: Review of technical documents and records, post-marketing surveillance inspection records, and Pharmacy and Poisons Board (PPB)quarterly, annual or mid-term reports.*
- *Semiformal or formal discussions and consultations: Discussion shall be held with responsible officials within the stakeholders*
- *Field inspection: To collect data*
- *Existing post-marketing surveillance data: quantitative data on IVD samples and test results from field operations shall be considered*

5.2. DATA ANALYSIS, REPORTING, AND PRESENTATION

Both qualitative and quantitative data collected for each indicator shall be examined, analyzed, and where appropriate, computed into percentages. Where necessary and appropriate, these data shall be presented in tables or other graphic depictions for better visual data comparisons.

In the analysis, both the number and proportion (numerator/denominator) expressed as a percentage (%) shall be used for selected indicators.

Numbers shall also be used to explicitly reflect the actual data.

5.3. POST MARKET SURVEILLANCE INDICATORS

INDICATOR	SOURCE	FREQUENCY	RESPONSIBILITY
1.0 PROCESS INDICATOR			
Number of IVDS sampled and analyzed	Testing reports	Bi-annually	Regulatory bodies National reference labs
Number of complaints on IVD	complaints received	Weekly	End-user
2.0 STRUCTURAL INDICATORS			
Number of lot-to-lot verification done on the IVD	Lot-to-lot verification reports	Bi-annually	National reference lab
Number of EQA cycles done and passed	EQA reports	Bi-annually	National reference lab
Number of IVDS reported failing due to poor storage conditions	Non-conformity reports	Weekly	End-user
3.0 OUTPUT INDICATORS			
Number of personnel trained(based on needs assessment) in conducting PMS on IVDS	Training log	Quarterly	Technical advisory committee
4.0 OUTCOME INDICATORS			
A reduction in the number of complaints on defective IVDS	Complaints received	Quarterly	End-user
5.0 IMPACT INDICATORS			
Number of reported casualties resulting from the use of faulty IVDS	Incidence reports	Quarterly	End-user
Number of IVDS recalled	Incidence reports	Quarterly	End-User

6. APPENDICES

Appendix 1 – Lot Testing Data Collection Form

Date tests received	dd/mm/yyyy
Test date	dd/mm/yyyy
Product name	[add product name]
Distributor/importer name and address	[add name and complete street address, email, phone]
Product code	[add product code]
Expiry date	dd/mm/yyyy
Lot number	[add]
Pre-distribution [tick one]	Post-distribution lot testing [tick one]
Name and signature of operator	
Signature of technical supervisor	

If subjectively read assay – ensure that specimens are run in a randomized manner. This template is for illustrative purposes.

Panel Specimen ID	Test results		Lot testing result	Reference result
	Reading 1	Reading 2		
Expand as required				

Appendix 2 – Testing Report Format For Lot Verification Testing

1. General information about the lot testing event

Date tests received	dd/mm/yyyy
Test date	dd/mm/yyyy
Product name	[add]
Distributor/importer name and address	[add]
Product code	[add product code]
Expiry date	dd/mm/yyyy
Lot number	[add]
Pre-distribution lot testing [tick one]	Post-distribution lot testing [tick one]
Laboratory performing the testing	[name of testing laboratory]
Site test kits were sampled from	[add site name]
Report number	[add report number assigned by testing laboratory]
Report date	dd/mm/yyyy
Responsible person	[add name]

The objective of lot testing is to verify the performance of the IVD and to ensure that it continues to meet WHO requirements for prequalification by identifying any form of product failure.

Appendix 3: Reference documents

The following reference documents have been used in preparing this document. ISO 9001:2008 Quality management systems requirements

ISO15189:2012 Medical laboratories requirements for quality and competence

ISO 13485:2003 for Medical devices

ISO 14971:2007 Medical devices - Application of risk management, which outline their requirements for compliance with post-market surveillance aspects of these standards

WHO Guidance for post-market surveillance and market surveillance of medical devices, including in vitro diagnosticsWHO dentitions: emergencies. Geneva: World Health Organization; 2020 (https://www.who.int/hac/about/dentitions/en/, accessed 29 January 2021).

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