REPUBLIC OF KENYA
MINISTRY OF HEALTH
KENYA MEDICAL LABORATORY TECHNICIANS AND TECHNOLOGISTS BOARD
PROCEDURE VERIFICATION AND VALIDATION OF INVITRO DIAGNOSTICS (IVDS) IN KENYA

Pursuant to the Medical Laboratory Technicians and Technologists Act,CAP 253A Laws of Kenya.

KMLTTB QUALITY ASSURANCE SERVICES

KENYA MEDICAL LABORATORY TECHNICIANS AND TECHNOLOGISTS BOARD *Make Testing a Safe Reality*	PROCEDURE VERIFICATION AND VALIDATION OF INVITRO DIAGNOSTICS (IVDS) IN KENYA		DOCUMENT CONTROL Serial: KMLTTB/VER/VAL/PROCEDURE/01
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A. PROCEDURE OF VERIFICATION AND VALIDATION OF INVITRO DIAGNOSTICS IN KENYA.

INTRODUCTION

The Kenya Medical Laboratory Technicians and Technologists Board (KMLTTB) is a statutory body mandated to oversee the training, practice, business, and employment of medical laboratory technicians and technologists, as stipulated under Cap 253A of the Laws of Kenya. The Board also provides government advisories on related matters, including the validation of in vitro diagnostics through Legal Notice No. 113 of 2011.

The Act gives the Board the responsibility of ensuring that all medical laboratories undertaking medical laboratory analysis and investigations are duly inspected so as to meet the required standards including use of validated and verified invitro diagnostics (IVDs).

These standards will ensure the development of a robust quality assurance medial laboratory services necessary to meet national and international health obligations that include sustainable development goals and universal health coverage. The implementation of this procedure guideline will no doubt contribute to achievement of the right to the highest attainable standard of health as outlined in the constitution of Kenya 2010 as well as achievement of Vision 2030.

All medical laboratory institutions and other key actors are required to adhere to the required scientific standards of IVDs validation and verification so as to ensure professionalism that guarantees the public of their right to highest attainable standards of healthcare, patient safety as well as safety for medical laboratory professionals and the environment

This procedure has been developed for verification and validation of IN VITRO DIGNOSTICS (IVDs) for approval in Kenya pursuant to section 5 (e), 25(2)(a) and 40(d) of Medical Laboratory Technicians and Technologist Act Cap 253A Laws of Kenya.

The scientific verification and validation (V&V) of a new In Vitro Diagnostic (IVD) device by **KMLTTB through approved /registered** medical laboratories, for in country use, requires a rigorous process ensuring the device meets performance claims (**verification)** and is fit for its intended clinical purpose **(validation).** This process is governed by standards such as **ISO 15189:2022** and other regulatory procedures.

The following is a detailed procedure for this process, broken down into analytical verification (reproducing manufacturer claims) and clinical validation (testing clinical performance).

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1. PREPARATION AND PLANNING PHASE

a) **Establish Intended Purpose:** Clearly state and define what the IVD measures (analyte), the sample type (e.g., serum, whole blood), the patient population, and the clinical intended use.

b) **Documentation Review:** Review the manufacturer's Instructions for Use (IFU), certificates of analysis, and technical data.

c) **Risk Assessment:** Perform a risk analysis (e.g., ISO 14971) to identify potential failures in the analytical process and patient impact, especially when used for in country use. Identify potential failure points (e.g., cross-reactivity, stability issues) and mitigation strategies

d) **Protocol Development:** Write a formal **Validation Plan** outlining acceptance criteria (e.g., "Must achieve >95% sensitivity"), statistical methods, sample sizes, and required personnel training.

2. ANALYTICAL VERIFICATION (METHOD VERIFICATION)

Verification ensures the device performs according to the manufacturer's specifications in the medical laboratory's specific environment.

a) **Precision/Reproducibility:** Perform experiments to test within-run and between-run precision using control materials. Running the same sample multiple times within a day (intra-assay) and over several days (inter-assay) to calculate the **Coefficient of Variation (%CV)**.

b) **Trueness/Accuracy:** Compare the new IVD against a reference method or a previously validated method. Testing certified reference materials or comparing results against a "gold standard" method.

c) **Precision (Repeatability/Reproducibility): Limit of Detection (LoD) & Limit of Quantitation (LoQ): This is to d**etermining the lowest concentration the test can reliably detect and measure**. This will** verify that the test can measure across the claimed range, particularly at the low (limit of detection) and high ends.

d) **Analytical Specificity (Interference):** Test the effect of potential interferents (e.g., hemolysis, icterus, lipemia) on test results. This involves testing for **interfering substances** (e.g., bilirubin, lipids) and cross-reactivity with similar analytes.

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e) **Carryover:** Evaluate if high-concentration samples contaminate subsequent low-concentration samples, if applicable.

3. CLINICAL VALIDATION

Validation confirms that the IVD fulfills its intended clinical purpose in the hands of the medical laboratory professionals. Verification proves the medical laboratories can replicate the manufacturer's claims. Key metrics include:

a) **Clinical Performance Study:** Use patient samples (characterized) to calculate clinical sensitivity (ability to detect disease) and clinical specificity (ability to identify healthy individuals). This will determine **Clinical Specificity, where t**he ability of the test to correctly identify those **without** the disease. And **Predictive Values (PPV/NPV), where** assessment of the likelihood that a positive or negative result is actually correct within a specific population.

b) **Method Comparison:** Compare results with a recognized "gold standard" or diagnostic, measuring positive/negative predictive values.

c) **Usability Testing:** Ensure the intended users (Registered and licensed medical laboratory professionals) can correctly follow the procedure, manage samples, and interpret data.

4. SPECIAL CONSIDERATIONS FOR IN COUNTRY USE

a) **Method Transfer:** If the method was developed elsewhere, perform a formal method transfer protocol to ensure the **in country** medical laboratories can replicate performance.

b) **Software Validation (CSV):** If the IVD includes software, conduct Computerized Systems Validation (CSV) to confirm accurate data handling and LIS integration.

c) **Stability Studies:** Evaluate the stability of reagents after opening, storage stability, and sample stability. This involves verifying the "on-board" and shelf-life stability under laboratory conditions, determining how long a specimen remains viable at room temperature, refrigerated, or frozen. And testing small variations in the environment (e.g., temperature, humidity) or operator technique to ensure consistent performance.

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5. DOCUMENTATION AND APPROVAL

a) **Data Analysis & Statistics:** Compile all data and perform statistical analysis (e.g., Passing-Bablok regression, Bland-Altman plots) **Traceability Matrix:** Create a document mapping each requirement to a specific test result to show compliance.

b) **Sign-Off:** The medical Laboratory Director reviews and signs off on the final V&V report, recommending to KMLTTB the method "Ready for Clinical Use" in the specific medical laboratory.

c) **SOP Implementation:** Create the Standard Operating Procedure (SOP) for routine testing based on the validated method including **Quality Control (QC)** intervals.

6. POST-VALIDATION MAINTENANCE

a) **Internal Quality Control (IQC):** Implement a daily QC program.

b) **External Quality Assessment (EQA):** Participate in proficiency testing to compare performance with other medical laboratories in the country.

7. KEY STANDARDS MENTIONED:

- **ISO 15189:2022** (Medical laboratories - requirements for quality and competence).

B. SCIENTIFIC VERIFICATION AND VALIDATION (V&V) FOR A NEW INTERNAL-USE IN VITRO DIAGNOSTIC (IVD), (MEDICAL LABORATORY DEVELOPED TEST (LDT))

Scientific Verification and Validation (V&V) for a new internal-use In Vitro Diagnostic (IVD), often referred to as a medical laboratory developed Test (LDT), is a rigorous process to ensure the method is fit for its intended clinical purpose. While **verification** confirms that a medical laboratory can replicate established performance claims, **validation** is the deeper process of establishing those performance characteristics for a new or modified method.

1. PLANNING AND PRE-ANALYTICAL REQUIREMENTS

Before testing begins, the medical laboratory must establish a formal Validation Master Plan (VMP). This protocol must be approved by the medical Laboratory superintendent/ Director.

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a) **Define Intended Use**: Explicitly state what the test measures, the target population, and the clinical purpose (e.g., screening vs. diagnosis). Ensure the method is fully developed, stabilized, and optimized

b) **Standard Operating Procedure (SOP)**: A fully optimized, written protocol must be available before validation starts.

c) **Equipment Qualification**: Ensure all instruments (pipettes, analyzers, etc.) are calibrated and maintained. Ensure stable, appropriate, and traceable materials are available.

d) **Personnel Training**: Staff must be trained and their competence documented specifically for this new method.

2. ANALYTICAL PERFORMANCE VERIFICATION (VERIFICATION)

This phase proves the "ability of a device to correctly detect or measure a particular analyte". Key parameters should include:

a). Accuracy (Trueness and Precision):

Goal: Determine if the new method correlates with a reference method or gold standard.

I. **Trueness**: Comparison against a reference standard.

II. **Precision**: Evaluation of repeatability (within-run) and reproducibility (day-to-day/operator-to-operator). Analyze 40–100 patient samples covering the entire range (low, normal, high).

b). Linearity and Measuring Interval: For quantitative tests, determine the range where results are directly proportional to analyte concentration.

c.). Detection Capability: Establish the Limit of Detection (LoD) and Limit of Quantitation (LoQ). Use Passing-Bablok or Deming regression to calculate bias

d). Analytical Specificity: Test for interferences (e.g., hemolysis, icterus, lipemia) and cross-reactivity with similar substances. Slope 0.9–1.1, intercept close to 0,

2. PRECISION (REPRODUCIBILITY & REPEATABILITY)

a) **Goal:** Measure the consistency of the results.

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b) **Protocol:** Run at least 2–3 control levels, 2 runs per day, over 5–20 days.

c) **Data Analysis:** Calculate within-run (repeatability) and total precision (CV%).

d) **Acceptance Criteria:** CV% below the maximum allowable coefficient of variation.

3. ANALYTICAL SENSITIVITY (LOB, LOD, LOQ)

a) **Limit of Blank (LoB):** Measure blank samples to determine the highest signal expected.

b) **Limit of Detection (LoD):** The lowest concentration detectable.

c) **Limit of Quantitation (LoQ):** The lowest concentration that can be measured with acceptable precision/bias.

4. ANALYTICAL SPECIFICITY (INTERFERENCE & CROSS-REACTIVITY)

a) **Goal:** Assess if endogenous/exogenous substances affect results.

b) **Protocol:** Test samples with high levels of hemolysis, icterus, lipemia, or common drugs.

c) **Acceptance Criteria:** Deviation from control samples must be within accepted limits.

5. LINEARITY AND REPORTABLE RANGE

a) **Goal:** Confirm accuracy across the intended measurement range (AMR).

b) **Protocol:** Create a serial dilution series of a high-concentration sample.

c) **Data Analysis:** Perform linear regression.

d) **Acceptance Criteria: Quality Control (QC):** Establish internal QC (IQC) procedures, including frequency of running controls.

e) **External Quality Assessment (EQA):** Enroll in proficiency testing, if available.

f) **Continuous Monitoring:** Periodically review performance data and, if necessary, revalidate.

6. REFERENCE INTERVAL (NORMAL VALUES)

a) **Goal:** Establish the range for healthy individuals.

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b) **Protocol:** Test at least 20–100 individuals from the target population

7. CLINICAL PERFORMANCE VALIDATION (VALIDATION)

This phase assesses whether results correlate with a specific clinical condition in real-world conditions.

a) **Clinical Sensitivity/Specificity**: The proportion of positive/negative results correctly identified compared to a clinical reference standard.

b) **Sample Selection**: Use a sufficiently large, well-characterized collective of human patient samples representative of the target population.

- *Validation Minimums*: **Often suggested at ≥50 positive and ≥100 negative specimens.**

C. Reference Intervals: Verify or establish the "normal" range for the specific laboratory population. .

8. VERIFICATION OF PERFORMANCE SPECIFICATIONS

If the manufacturer has provided performance claims (for a CE-IVD assay used outside its intended scope), the laboratory must *verify* that it can achieve those claims in their own hands.

a) **Protocol:** Limited validation (e.g., precision and accuracy on 20 samples).

9. POST-ANALYTICAL AND ONGOING REQUIREMENTS

a) **Validation Report**: Summarize all data, statistical analyses, and conclusions. The medical Laboratory superintendent/director must review and sign this report before the test goes live.

b) **Stability Studies**: Demonstrate reagent shelf-life and stability under typical storage/transport conditions.

c) **Post-Market Surveillance**: Implement a plan for ongoing monitoring via internal quality control (IQC) and External Quality Assessment (EQA)

d) **Documentation:** All raw data, statistics, and deviations must be recorded.

e) **Sign-off:** The final validation report must be approved by the Laboratory Director, authorizing the method for clinical use

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