ICMR-CDSCO STANDARD PERFORMANCE EVALUATION PROTOCOLS

ANALYTICAL PERFORMANCE EVALUATION OF IN-VITRO DIAGNOSTICS FOR PULMONARY TUBERCULOSIS

ICMR-CDSCO/IVD/TB/PROTOCOLS/1/2025

DIVISION OF COMMUNICABLE DISEASES, ICMR
IN VITRO DIAGNOSTICS DIVISION, CDSCO

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India

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Analytical Performance Evaluation of IVD for Pulmonary Tuberculosis

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I. Background

CDSCO and ICMR, New Delhi, have aimed at facilitating the availability of Quality-Assured diagnostic kits appropriate for use in India. This protocol gives the methods to be used for evaluating the analytical performance characteristics of the in-vitro diagnostic test in detecting pulmonary tuberculosis and drug-resistant tuberculosis.

Note: According to CDSCO guidelines, "performance evaluation" refers to "analytical validation" required for obtaining "test license", while “field evaluation” refers to "clinical validation” performed in clinical samples in real world setting.

II. Purpose

To evaluate the performance characteristics of nucleic acid amplification tests (NAAT) forthe diagnosis of pulmonary Mycobacterium tuberculosis (MTB) using irreversibly de-identified leftover archivedor spiked sputum samples.

III. Study Design

Analytical validation of IVD using irreversibly de-identified leftover clinical/spiked samples.

IV. Ethical Considerations

1. Leftover sputum specimens collected for routine diagnostic evaluation from patients who are suspected of having TB shall be used. No additional specimens should be requested.
2. The probability of harm or discomfort anticipated in the research is nil or not expected.
3. Performance evaluation activities using irreversibly de-identified leftover clinical samples are exempt from ethics approval as per ICMR’s Guidance on Ethical Requirements for Laboratory Validation Testing, 2024.
4. Investigators are required to submit a self-declaration form, as outlined in the ICMR guidelines, to the institutional authorities and ethics committee for information.
5. The protection of privacy of participants should be ensured by using de-identified samples and encrypting the patient identifiers.
6. Respect for the dignity of participants shall be prioritized.

V. Blinding of Laboratory Staff

To ensure the rigor of the evaluation process, laboratory staff performing the evaluation should be blinded to the status of the clinical samples. The PI of the evaluation exercise should remain unblinded, i.e., privy to the status of the samples. Another senior laboratory staff member selected by the PI may remain unblinded and carry out coding of samples and dispensing them into similar-looking vials to be used for testing, and maintain the database of results. Staff performing the reference test and the test under evaluation, interpretation of the test result, and entering the results against the coded samples in the database, should remain blinded to the status of samples till the completion of evaluation. The data should be analyzed only by the PI of the evaluating lab. Refer to Fig. 1.

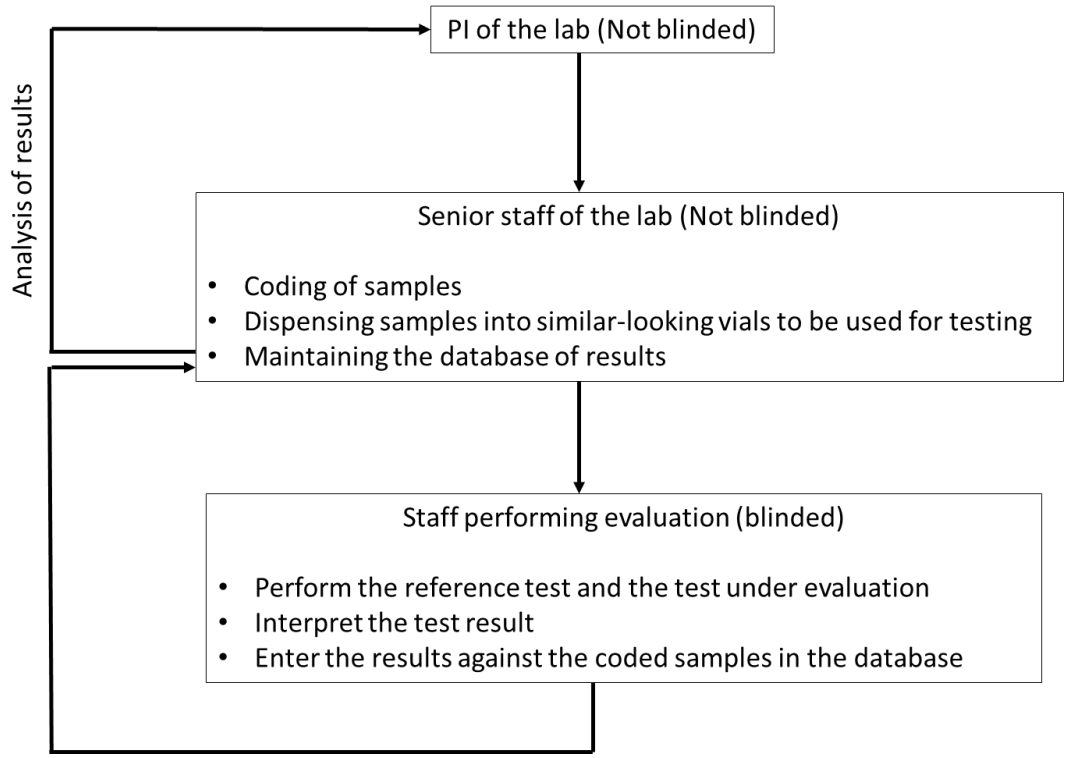


Figure 1 Blinding in evaluation exercise

VI. Procedure

1. Preparation of Evaluation sites/laboratories

A. The laboratory must be approved by the National TB Elimination Program (NTEP).

B. Accreditation for at least one Quality management system [accreditation for Testing Lab / Calibration Lab (ISO/IES 17025), Medical Lab (ISO 15189), PT provider ISO/IEC 17043 or CDSCO approved Reference laboratory].

2. Exclusion

- Extra-pulmonary samples
- Specimens with > 1 freeze-thaw cycle (or according to IFU, if specified)
- Any exclusion criteria stated in the product IFU

3. Reference tests

- ***For detection of MTB:*** Mycobacterium Growth Indicator Tubes (MGIT) liquid culture.
- ***For MDR-TB:*** MGIT drug sensitivity testing (DST)

4. Preparation of samples

- ***For LOD studies - MTBC-negative sputum:*** smear-negative and NAAT-negative sputum should be used for the spiking analytic studies
- ***For analytical sensitivity and specificity:*** Well characterized archived samples (sputum or processed sputum); MTB positives, MTB negatives and Non-Mycobacterium tuberculosis (NTM) samples confirmed by liquid MGIT culture
- ***For drug sensitivity:*** MTB and NTM clinical isolatesthoroughly characterized through MGIT DST and sequencingshould be used.
- For inclusivity/exclusivity, resistance detection, and cross-contamination, mycobacterial strains should be diluted into 7H9 medium at the required concentrations.
- The concentrations (cfu/mL) should be estimated by adjusting the bacterial suspension density to the McFarland standards.

5. Reference Strains

The National Institute for Biological Standards and Control (NIBSC) internal reference standard for Mycobacterium tuberculosis (H37Rv) DNA for Nucleic Acid Amplification Test (NAAT) based assays (NIBSC code: 20/152) will be used for the LOD assay. It was established as the 1st WHO International Standard for Mycobacterium tuberculosis (H37Rv) DNA for NAAT-based assays in 2021. The intended uses of this material are for calibration of secondary or in-house reference materials used in the assays for the molecular detection of *M. tuberculosis* DNA.It may also be used for assay validation and monitoring the limit of detection of rapid diagnostic tests. This preparation contains an arbitrary unitage of 6.3 log10 (or 2 million) IU per vial.

6. Sample size and sample panel composition

With an anticipated sensitivity of 90% and relative precision of 7%, a minimum of 87 confirmed MTB positive samples by MGIT culture will be required for testing analytical sensitivity. With an anticipated specificity of 95% with 5% relative precision, the minimum sample size required for analytical specificity is 81 confirmed MTB negative samples by MGIT culture. To rule out NTM detection, with an assumed sensitivity of 90% and relative precision of 10%, around 50 confirmed NTM samples may be included to evaluate the index test kit. Hence, approximately 100 confirmed MTB positives, 100 confirmed MTB negatives and 50 NTM samples will be used for pre-validation studies.

The proposed evaluation study will be done using Sputum/MTB isolates stored at the biobank facility of the National TB reference laboratories (NRLs) or the pre-validation labs. The stored sputum/MTB isolate/processed sample/DNA samples will be of the following categories and sub-categories.

Category 1: Positive for MTB by MGIT culture (N = 100) [MTB positives should include equal number of low, medium and high bacterial load samples demonstrated by Xpert MTB]

Category 2: Negative for MTB by MGIT culture (N = 150)

Within the MTB negative group, we propose the following two sub-categories:

i. Negative for all Mycobacteria (N = 100)
ii. Positive for Non-Tuberculous Mycobacterium (N = 50)

Equivalence studies:

If a new specimen or format needs to be evaluated for an already recommended IVD, an equivalence study may be performed with 50 MTB positive and 50 MTB negative specimens to establish relationship between IVD performance in the newly claimed specimen type or new format of same technology. However, if the technology used for the IVD design is different, it shall go through the full process of validation.

Category 3: If resistance detection has to be carried out, within the MTB positive group, we propose to use the following sub-categories:

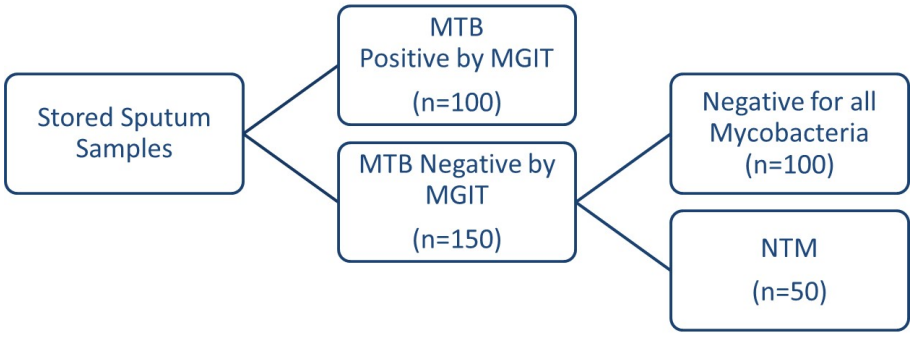
i. Sensitive to Rifampicin and Isoniazid, individually and combined (N =100) confirmed by Drug susceptibility testing on MGIT liquid culture.
ii. Resistance to both Rifampicin and Isoniazid (N = 100) as detected by Drug susceptibility testing on MGIT liquid culture.
iii. Isoniazid mono-resistance (N =45) as detected by DST on MGIT liquid culture.
iv. Fluroquinolone resistance (N=45) (if applicable for the index test) as confirmed by DST on MGIT liquid culture.

Table 1: Sample size calculation with 95% confidence level

Anticipated Sensitivity	Relative Precision	Sample size
90%	5%	171
90%	10%	43
90%	7%	87
95%	5%	81
95%	10%	20
95%	7%	41

Analytical sensitivity and specificity:

a)



b)

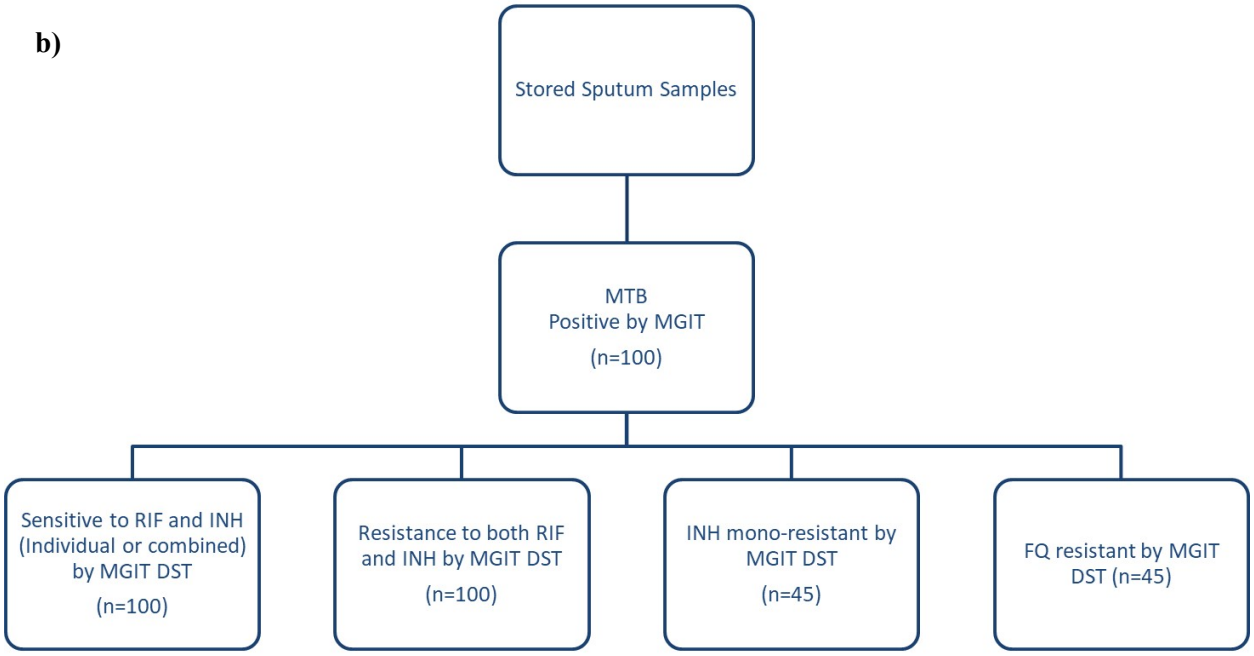


Figure 2. Flowchart for Analytical Performance Evaluation for detection of; a) MTB detection, b) MDR-TB

7. Limit of Detection (LOD) Assay

The 95% LOD is defined as the minimum concentration of bacterium, expressed as CFU/ml or genomic DNA copy numbers/mL, in a sample volume that can be detected in 95% of tests. Finalize the LOD at least one concentration with a hit rate above 95% and two concentrations with hit rates between 10% and 90%. LOD should be always done with NIBSC H37Rv (20/152) standard and only reported in IU/ml or CFU/ml.

Preparation of samples for LOD

1. The volume of sputum required for LOD is based on the IFU (Instruction for use) from the index test manufacturer, which generally varies between 1-2 ml of sputum.
2. A minimum of 200ml of NAAT negative sputum is required for the full LOD studies for a single index test.
3. Sputum samples which are negative by Xpert MTB will be stored at -20^{o}C and once the required amount is obtained the samples will be pooled and tested for MTB using molecular and phenotypic test to prove no growth of MTB in the pooled samples.
4. To perform the assay it may take two weeks to one month based on the multiplicities of test suggested in the IFU after the required volume of sputum is collected.

Spiking of sputum samples

1. The spiked sputum will be used *to determine th*e LOD of the test kit. About 1.8 ml of negative sputum *specimen will* be spiked with 200 ul of the respective diluted suspension series of *M. tuberculosis* H37Rv.
2. These dilutions will be added to the sputum to get the final concentration (10000, 1000, 100, and 10 IU/ml). Before spiking, the culture for CFU wil*l be set up for* the different dilutions.
3. NIBSC reference standard will be reconstituted as directed by NIBSC using 1 mL nuclease free molecular biology grade purified water (MBGPW). From this stock 100 µL will be diluted ½ to get 10,00,000 IU/ml and serially diluted to give 100000, 10000, 1000 and 100 IU/ml with MBGW.
4. Each dilution of the WHO International Standard, will be tested 24 times. The 24 replicates will be performed over at least three days by at least two users and, for low-throughput instruments, on at least three different instruments, or sets of instruments if applicable (e.g.,

DNA preparation and amplification instruments). For low through-put instruments, the number of testing days may be increased.

5. When *M.tuberculosis* (H37Rv) is used, the 24 replicate tests shall comprise (8 replicate tests on each day for 3 days) of a minimum 8-member 0.5 log 10 dilution panel of a suitable biological reference material (e.g., WHO International Standard) (WHO TSS-17).
6. Each lot shall comprise different production (or manufacturing, purification, etc.) runs of critical reagents. Inter-lot variation must be evaluated by appropriate statistical means.
7. Lowest dilution at which the test detects M.t*b will be deter*mined a LOD, the corresponding CFU will also be counted and reported in terms of CFU/per ml. The LOD will be presented as IU/mL for each dilution.
8. Analytical sensitivity shall be estimated by determining the 95% LOD with 95% confidence intervals (e.g., by probit analysis).
9. If there are more than four invalid results with the same specimen (i.e. dilution) overall, then the specimen will be retested to get at least 20 valid results for each dilution. For tests that include a claim for drug resistance testing, at least 20 valid results (i.e., sensitive or resistant) for each of the claimed drugs should be obtained for each dilution.
10. To arrive at the LOD a probit analysis should be performed, Probit analysis is defined as a specialized form of regression analysis applied to binomial response variables, transforming a concentration-response curve into a straight line for analysis through methods like least squares or maximum likelihood regression. It is primarily used in molecular biology measurement procedures, such as PCR, to determine the detection probability of analytes at various concentrations.

LOD for detection of drug resistance

1. To test the drug resistant MTB strains, well-characterized MTBC strains of known concentration (expressed as CFU/mL) shall be spiked into each claimed MTBC negative specimen type. DR strains shall be characterized by sequencing.
2. Relevant DR strains (as mentioned in table below) shall be spiked into each claimed MTBC-negative specimen type (e.g., raw and/or processed sputum, and each claimed extra-pulmonary specimen).

3. If the assay detects resistance to more than 1 target drug, the LOD for each target drug in addition to a composite resistance LOD, defined as the highest LOD among the tested target, shall be reported.
4. Analytical sensitivity for resistance detection shall be estimated as the lowest number of colony-forming units (CFU) per specimen that can be reproducibly distinguished from negative specimens with 95% confidence.
5. The determination shall comprise 24 replicate tests (8 replicate tests on each of 3 days) of a minimum 8 8-member 0.5log10 dilution panel. The replicate testing shall be conducted on three different days using 2 lots, and at least 2 dilution series shall be tested.

Table 2: Anti-mycobacterial drugs and common mutations

S.No	Drugs	Resistance mutation of strains to be tested
1	Isoniazid	katG_S315T and fabG1_c-15t
2	Rifampicin	rpoB_S450L; rpoB_D435V; rpoB_H445Y; rpoB_H445D; rpoB_D435Y; rpoB_S450W; rpoB_L452P; rpoB_H445L; rpoB_S450F; rpoB_L430P; rpoB_H445R; one rpoC mutation
3	Levofloxacin (CC) LFX2,3	gyrA_A90V, gyrA_D94G, gyrA_D94H, gyrA_D94N, gyrA_D94Y, gyrA_S91P
4	Moxifloxacin (CC and CB)	gyrA_A90V, gyrA_D94G, gyrA_D94H, gyrA_D94N, gyrA_D94Y, gyrA_S91P
5	Bedaquiline	Rv0678_LoF, pepQ_LoF, atpE_p.Ala63Pro
6	Linezolid	rplC_p.Cys154Arg, rrl_n.2814G>T
7	Ethambutol	embB_M306L, embB_M306V, embB_Q497R
8	Delamanid	ddn_LoF, ddn_p.Leu49Pro, fbiC_LoF
9	Pyrazinamide	pncA_ V139A, pncA_ V139G
10	Amikacin	rrs_ A1401G, rrs_ A1401G, rrs_G1484T, eis /promoter_ C-12T, eis /promoter_C-14T
11	Kanamycin	rrs_ A1401G, rrs_ A1401G, rrs_G1484T, eis /promoter_ C-12T, eis /promoter_C-14T
12	Capreomycin	rrs_ A1401G, rrs_ A1401G, rrs_G1484T, eis /promoter_ C-12T, eis /promoter_C-14T
13	Ethionamide	fabG1_c-15t, inhA_S94A, fabG1_ T-8C

14	Pretomanid[#]	ddn_LoF, ddn_p.Leu49Pro, fbiC_LoF
15	Cycloserine	Alr_C-8T, alr_M319T, alr_Y364D, ald_T-32C, ddlA T365A
16	PAS	thyA T22A, folC I43T, folC R49W

8. Reproducibility

Three lots of a test shall be evaluated for lot-to-lot reproducibility. Each lot will comprise different production (or manufacturing, purification, etc.) runs of critical reagents.

- First lot of the assay: should be tested on statistically significant number of positive and negative samples as calculated in the protocol.
- Second lot of the assay: should be tested on 20 samples (10 MGIT positive samples and 10 MGIT negative samples).
- Third lot of the assay: should be tested on 20 samples (10 MGIT positive samples and 25 MGIT negative samples).

Within-run (same operator, same measuring system, same operating conditions, and same location), Between-run, -lot, -day, -site, -operator.

1. Three specimens will be used; MTB sensitive (H37Rv), MTB resistant and MTB negative.
2. The effect of operator-to-operator variation on IVD performance will be included as part of the precision studies.
3. The nucleic extraction/purification component will also be considered for estimating precision.
4. Contrived specimens will be used (i.e., MTBC strains with specific/most common mutations in the target genes spiked into a clinical matrix claimed in the IFU) for repeatability and reproducibility studies.
5. DR specimens at the concentrations specified for each DRTB (i.e. RR-TB, Hr-TB, MDR-TB, TB resistant to fluoroquinolones) as described in the table on resistance detection.
6. If there are two or more invalid results for the same specimen in the same run, then the run should be repeated for this specimen. Invalid results should be reported.
7. Results will be statistically analyzed by ANOVA or other methods to identify and isolate the sources and extent of any variance.

8. Furthermore, the percentage of correctly identified, incorrectly identified, and invalid results will be compiled for each specimen and separately categorized by site, lot, and other factors.
9. Within-run and within-laboratory reproducibility will be assessed by measuring eight replicates. At least two operators will test a total of 40 positives and 40 negatives with two batches of the kit over a period of 5 days.

9. Inclusivity and exclusivity

1. Inclusivity MTBC stains: For a claim of MTBC detection, the following strains shall be tested: *M. tuberculosis, M. bovis, M. bovis BCG, M. africanum, M.microti and M.caprae*
2. Exclusivity NTM strains: *M. avium, M. kansasii, M. intracellulare*
3. Representative MTBC and non-tuberculosis mycobacteria (NTM) strains will be tested in triplicate forinclusivity and exclusivity verification.
4. Resistance detection: For assays with a claim for detection of drug resistance, the applicable specimens from the resistancedetection panelwill be tested in triplicate.
5. The concentration of MTBC isolates used in inclusivity studies will be at levels at or near the specific LOD and will be confirmed by plating/ counting bacterial CFUs (estimated using Truenat).
6. The selection of specific MTBC strains with relevant genetic variations linked to DR will be made to support the claims in the IFU.
7. This will involve testing strains that carry the most common mutations, including associated or interim resistance mutations, covering at least 80% of the resistance mechanisms observed globally for each of the assay target drugs (as shown in table 2).

10. Cross-contamination/carry-over

1. The experiment will allow the determination of the well-to-well or vial-to-vial cross-contamination rate ofhigh-throughput platforms or potential carryover in low-throughput instruments.
2. This will be assessed byalternating one high-positivespecimen with one negative specimen and repeating thissequence twenty times.
3. For high-throughput assays, this will be achieved by alternating high-positive andhigh-

negative specimens in the same plate/run.

4. For low-throughput assays, each sequence of highly positivespecimens followed by negative specimens should be done on the same instrument.
5. If more than one instrument isused, each run (i.e same instrument and same day) should include a minimum of 2 sets of alternating high-positive and negative specimens.
6. Contrived specimens prepared by spiking MTBC strains into MTBC negative clinical sputum will be used for these studies.

Note: The strains used for assessment of reproducibility, inclusivity/exclusivity, resistance detection, and carry-over may be commercially acquired or locally prepared, well-characterized strains (by phenotypic DST and sequencing).

11. Resolution of discrepancy:

- The results of MGIT culture should be used to resolve any discrepancy in detection of MTB
- Results of phenotypic DST and sequencing should be used to resolve discrepancy in detection of MDR-TB.

VII. Statistical Analysis Plan

1. The index molecular test should be evaluated for its analytical sensitivity and analytical specificity.
2. 95% Confidence interval should be calculated for each of the parameters.

$$\% \text{ Sensitivity} = \frac{\text{Positives by index test}}{\text{Confirmed positives by MGIT culture}} \times 100 = [a/a+c] * 100$$

$$\% \text{ Specificity} = \frac{\text{Negatives by index test}}{\text{Confirmed negatives by MGIT culture}} \times 100 = [d/b+d] * 100$$

VIII. Acceptance Criteria

Acceptance criteria for Diagnostic tests:

Expected sensitivity: ≥ 90%

Expected specificity: ≥ 95%

Sample Size: ~ 100 confirmed MTB positives (by MGIT culture), ~ 100 confirmed MTB negatives (by MGIT culture) and ~ 50 NTM samples (confirmed by culture and identification)

Acceptance criteria for Screening tests:

Test Type	Minimal Accuracy	Optimal accuracy
High Sensitivity high specificity screening test	90% sensitivity 80% specificity	95% sensitivity 95% specificity
High Sensitivity screening test	90% sensitivity 60% specificity	95% sensitivity 85% specificity
High specificity screening test	60% Sensitivity 98% specificity	70% sensitivity 98% specificity

Source: WHO TPP 2025

IX. Publication Rights

The PI(s) of the evaluating labs shall retain publication rights of the evaluation as lead author(s).

IMPORTANT NOTE

Once a kit is determined to be "Not of Standard Quality", following the procedure outlined in this document, no further requests for repeat testing of that kit will be accepted. Any request of re-validation from the same manufacturer for the same test type will only be entertained after a minimum of 3 months and only if a high-level technical summary of modifications or functional improvements to the kit design is submitted, without explicit disclosure of proprietary information.

Clinical samples are precious, therefore, repeat evaluation of a kit using the same/ different well-characterized sample panel at a different laboratory may be considered only for kits which claim high performance characteristics (sensitivity and specificity 95% and above), but which fail the performance evaluation by a margin of 5%.

References

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5. WHO manual for the preparation of secondary reference materials for in vitro diagnostic assays designed for infectious disease nucleic acid or antigen detection: calibration to WHO International Standards. Available at: https://www.who.int/publications/m/item/annex-6-trs-no-1004

PERFORMANCE EVALUATION REPORT FORMAT

Performance Evaluation Report For MTB/MDR-TB Kit

Name of the product (Brand/generic)		
Name and address of the legal manufacturer		
Name and address of the actual manufacturing site		
Name and address of the Importer		
Name of supplier: Manufacturer/Importer/Port office of CDSCO/State licensing Authority		
Lot No /Batch No.:		
Product Reference No/ Catalogue No		
Type of Assay		
Kit components		
Manufacturing Date		
Expiry Date		
Pack size (Number of tests per kit)		
Intended Use		
Number of Tests Received		
Regulatory Approval: Import license / Manufacturing license/ Test license License Number: Issue date: Valid Upto:		
Application No.		
Sample Panel	Sample type	
	Positive samples (provide details: strong, moderate, weak)	
	Negative samples (provide detail: clinical/spiked, including cross reactivity panel)	

Results:

		Reference assay ……..…… (MGIT/MGIT DST for RIF/INH/FQ/others)		
		Positive	Negative	Total
Name of MTB or MDR-TB kit	Positive			
	Negative			
	Total			

	Estimate (%)	95% CI
Sensitivity		
Specificity		

Conclusions:

- Sensitivity, Specificity
- Performance: **Satisfactory / Not satisfactory**

(Sensitivity and specificity have been assessed in controlled lab setting using kits provided by the manufacturer from the batch mentioned above using ..... sample. Results should not be extrapolated to other sample types.)

DISCLAIMERS

1. This validation process does not approve / disapprove the kit design
2. This validation process does not certify user friendliness of the kit / assay

Note: This report is exclusively for ……Kit (Lot No……), version ……with the gene targets ……...manufactured by …… (Supplied by …….).

Evaluation Done on ……

Evaluation Done by …….

Signature of Director/ Director-In-charge …… Seal ……

**********End of the Report**********