I-TECH International Training & Education Center for Health

World Health Organization

On-site Training at
Takeo Provincial Hospital Laboratory
November 12-15, 2018

Method Verification/Validation

Ong Siew Kim
MS, MAACB, FAACB, MBA, PBT(ASCPi), EdD
Project Coordinator

Overview

Verification/validation evaluation

- Validation vs verification
- Studies & Activities
- Report writing
- SOP content

What is the difference?

- ✓**Validation:** objective evidence through a defined process that a test performs as intended [CLSI]
- ✓**Verification**: an abbreviated process to demonstrate that a test performs in substantial compliance to previously established claims

Note: Sometimes the term "validation" is used to cover both of the above—can be source of confusion

Definition according Food and Drug Administration (FDA)

- For tests approved by FDA—**verification** required:

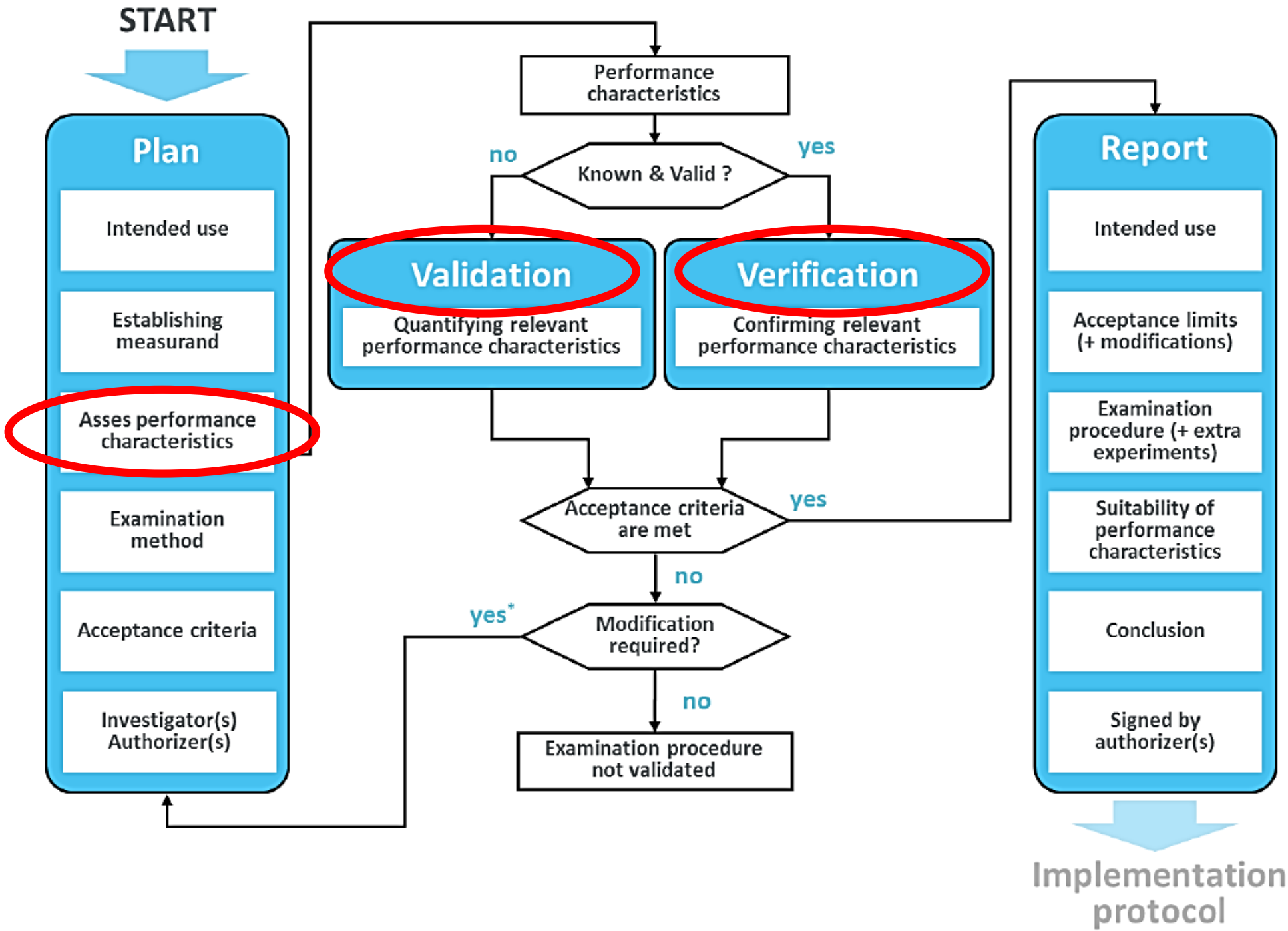
  laboratory must show that it can obtain performance specifications comparable to those established by the manufacturer.

- For tests not approved by FDA - **validation** required:

  laboratory must establish the performance specifications.

Does any lab use modified test?

- ***ISO15189:2012*** *Clause 5.5.1.2; 5.6.4 and 5.5.1.3 (CamLQMS)*
- **Validations** should be done on a) non-standard methods; b) laboratory designed or developed methods; c) standard methods used outside their intended scope; d) validated methods subsequently modified.
- **Verification** is performed on methods that are being used without any modifications and is a process of evaluating of whether or not the procedure meets the performance characteristics stated by the manufacturer i.e. the manufacturer validation claims. The performance characteristics are obtained from the manufacture (validation reports) or from package inserts. Comparison of different methods used for same tests is ongoing verification. The frequency and characteristics to be checked in ongoing verification must be clearly defined.
- Note: All procedures or equipment used as backup must also be validated/verified as relevant.


START
Plan
Intended use
Establishing measurand
Asses performance characteristics
Examination method
Acceptance criteria
Investigator(s) Authorizer(s)
Performance characteristics
Known & Valid ?
no
yes
Validation
Quantifying relevant performance characteristics
Verification
Confirming relevant performance characteristics
Acceptance criteria are met
yes
no
Modification required?
yes*
no
Examination procedure not validated
Report
Intended use
Acceptance limits (+ modifications)
Examination procedure (+ extra experiments)
Suitability of performance characteristics
Conclusion
Signed by authorizer(s)
Implementation protocol

What to do before you select a new analyzer?

1.5.27. Validation and Verification of examination procedures/Equipment

How the laboratory will:

1) select testing procedures;

2) perform equipment validation;

3) perform method validation;

4) perform equipment verification;

5) perform method verification;

6) define ~~validation/~~verification protocol specific for each procedure at the time of verification;

7) compare results from the different procedures, equipment, methods being used for the same test either located at the same site or at different sites?

What to do before you select a new analyzer?

1.5.27. Validation and Verification of examination procedures/Equipment

How the laboratory will: 1. select testing procedures

a. Selection of external services and supplier
b. Agreement with supplier
c. Nominate a staff to be in-charge
d. Create folder for the analyzer
e. Installation (calibration)
f. Training by the supplier
g. Create maintenance log
h. Familiarization (keep record with staff name and signature)
i. Write SOP (draft), final before submission to Lab/Hospital Director

What to do before you select a new analyzer?

1.5.27. Validation and Verification of examination procedures/Equipment

How the laboratory will:

2) perform equipment validation;

- Installation report by engineer
- Verify against the operator menu.
- Signed by engineer
- Sign by lab director

What to do before you select a new analyzer?

1.5.27. Validation and Verification of examination procedures/Equipment

How the laboratory will:

1) select testing procedures;

2) perform equipment validation;

3) ~~perform method validation;~~ if method is not modified √

4) perform equipment verification; Equipment operating menu, installation report.

5) perform method verification;

6) define ~~validation/~~verification protocol specific for each procedure at the time of verification;

7) compare results from the different procedures, equipment, methods being used for the same test either located at the same site or at different sites?

CamLQMS Section 5.3

Equipment and Method Validation/Verification and Documentation

- Are all equipment and methods validated/verified on-site upon installation and before use and is documented evidence available?

1. Are specific verification~~/validation~~ protocols in place for each equipment and examination procedure?
2. ~~Is validation performed for all laboratory designed or developed methods, standard methods used outside their intended scope and validated methods that are subsequently modified?~~
3. Has validation information been obtained from the manufacturer/method developer as part of the verification?
4. Have performance characteristics been appropriately selected and evaluated as per intended use?
5. Were the verification/~~validation~~ studies appropriate and adequate?
6. Was the analysis of data appropriate for the selected performance characteristics?
7. Have the verification results/reports been reviewed & approved by an authorized person?

When did we start the verification studies?

- September, 2018
- Mentor on-site Round 2
- Kg Cham On-site Internal Audit Training
- Zoom calls from Office

Method verification protocol

1. Measurement precision
2. Measurement trueness
3. Detection limits
4. Diagnostic characteristics
5. Analytical interferences
6. Carry-over
7. Stability
8. Verify all instrument measuring the same test
9. Implementation
10. Documentation

1. Measurement precision

- Run 3 times per day for 5 days (15 replicates for each level) 8am, 12pm, 4pm = 45 number of runs
- Repeatability (within day CV%),
- Reproducibility (between day CV%)
  - Calculate SD & CV (%) for the measurements,
  - Compare to manufacturer's claim (kit insert);
  - if higher, need to evaluate for cause

2. Measurement trueness

(method correlation; bias; reference material)

- Testing 20 samples that span the entire testing range (but do not exceed measurement range)
  - Low, medium, high concentration specimens
- Correlation of measurement and bias plot
- Linearity data: slope, intercept
- Bias = $\frac{\text{New method-old method}}{\text{Old method}} * 100$

3. Detection limits

(lowest level for detection; reportable range/recovery study)

- Involves two steps: determination of values obtained with blank samples, and values obtained with low level positive samples (CLSI EP17-A)

a. Run 20 blanks; if < 3 exceed stated blank value, accept that value

b. Run 20 low patient samples near the detection limit; if at least 17 are above the blank value, the detection limit is verified

c. Compare results with kit insert.

4. Diagnostic characteristics

(reference interval; medical decision level; reportable range/ recovery study)

a)Select 20 representative healthy individuals and do test; if ≤ 2 outside proposed limits, validated

b)If > 2 outside, can repeat with another 20, and accept if ≤ 2 outside (not worth repeat if > 5 outside proposed limits)

c)- Exclusion criteria: diseased, conditions as pregnancy, intense exercise, drug use or at risk individuals (e.g. obese)

-Partition criteria: age and sex

Recovery or linearity study

- The analytical measurement range (AMR) that a method can directly measure on the specimen .
- The clinically reportable range (CRR) that can measure through dilution.
- Verification of reportable ranges may not apply to certain assays (for example, in immunology and coagulation).
- Use highest concentration and dilute with low concentration specimens.
- Create 3 dilutions. Run each dilution test mix 3 times.
- Plot a theoretical and measured linear graph (slope 0.95-1.05).
- Compare the AMR with kit insert.

5. Analytical interferences

(hemoglobin interference)

Preparation

1. Use EDTA/heparin blood.
2. Measure Hb.
3. Wash rbc 3 times with saline.
4. Freeze packed rbc.
5. Thaw and centrifuge to obtain rbc.
6. Measure Hb concentration.
7. Use it to add to specimen.
8. Measure test analyte 3 times for each hemoglobin + specimen
9. Plot a graph of hemoglobin and test analyte concentrations
10. Verify kit insert claims.

6. Carry-over

- Run in sequence: 2 saline blank, 1 high specimen and 3 saline blank
- Acceptable if no carry over detected.
- Some analyzer do not need to do this study.

7. Stability

- Check on any significant change for sample, reagents, standards and controls.

  Example: any environmental changes that could affect the testing

8. Verify all instrument measuring the same test

(same lab or in different labs)

- Multiple instruments of same make & model: each must be verified separately.
- Interpretation:
  - accuracy could be verified for 2nd instrument by comparison study with 1st instrument (15-20 samples)
  - No separate reference range study needed for 2nd analyzer assuming comparison study showed absence of significant bias

9. Implementation

- Document training and running the new test.
- Evidence that the new test has been announced to the user.

10. Documentation

- Write a report on the verification of the new method/equipment
- Verification of compliance with performance targets
- Documentation must be signed by Lab / Hospital Director before test is being offered for service.

Write a report

1. Measurement precision
2. Measurement trueness
3. Detection limits
4. Diagnostic characteristics
5. Analytical interferences
6. Carry-over
7. Stability
8. Verify all instrument measuring the same test
9. Implementation
10. Documentation