Method Validation & Performance Verification:
Introducing New Analytes to Your Lab

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DISCLOSURE

Relevant Financial Relationships
None

Off Label Usage
None
Learning Objectives:

At the conclusion of this program the learner should be able to:

- Distinguish Validation from Performance Verification.
- Define “PARR”
- Describe test modifications which alter FDA approval, and therefore validation.
- Use the principles discussed to perform a Performance Verification in their Lab.
What is Validation?

“Validation is the process of testing a measurement procedure to assess its performance and to determine whether that performance is acceptable.”

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Technically speaking, **validation** applies to non-FDA approved testing and includes many additional studies. Manufacturers perform validation studies for new test kits.
Validation vs. Verification

*Performance verification* is the basis for our discussion today, and pertains to *only* FDA-approved or cleared test methodologies.

But many people use validation & performance verification interchangeably—"validation" is shorter!
Why Validation/Verification?

- CLIA regulations 493.1253[^3]:

  “The laboratory is responsible for verifying the performance specifications of each non-waived unmodified FDA-cleared or approved test system that it introduces, prior to reporting of patient results. The verification of method performance should provide evidence that the accuracy, precision, and reportable range of the procedure are adequate to meet the clients’ needs, as determined by the laboratory director...”

Note: these regulations do not apply to Waived Testing.
Why Validation/Verification?

College of American Pathologists (CAP) 
All-Common Checklist

- COM.40000- Method Validation Approval
- COM.40200- List of non-FDA Approved Tests
- COM.40300- Accuracy & Precision
- COM.40500- Analytical Interference
Why Validation/Verification?

College of American Pathologists (CAP): All-Common Checklist

- COM.40600-Reportable Range (AMR)
- COM.40700- Performance Verification Availability
- COM. 50000- Reference Interval Verification

*Note: Detailed validation requirements are found in the Microbiology checklist.*
Why Validation/Verification?

Joint Commission QSA.02.01.01:

“The laboratory verifies tests, methods, and instruments in order to establish quality control procedures. Note: This standard also applies to instruments on loan when the original instrument is under repair.”
Joint Commission  QSA.02.01.01

Elements of Performance

- **EP1**-Documented performance verification for FDA-approved methods.
- **EP2**-Non-FDA approved or *modified* methods (or those not subject to FDA approval) require written performance specifications.

**Note:** Effective 2/1/2012, interfering substances must be assessed with analytical specificity.
Joint Commission  QSA.02.01.01

Elements of Performance

- EP3- Documented correlation of old method to new method.
- EP4- Verification of reference intervals
- EP5- Verifications documented prior to patient testing.
- EP6- QC procedures established
- EP7- Specifications for QC
- EP8- Monitoring of performance over time
To What Does Verification Apply?

- All new FDA-approved instruments and/or test methods (non-FDA approved tests require additional studies) implemented after April 24, 2003\textsuperscript{3,6}
- Instruments which have been moved
- Loaner instruments
- Multiple new analyzers
- Each specimen type
So, what is Required?

“PARR”

- Precision
- Accuracy
- Reportable Range
- Reference Range

Note: PARR is the minimum requirement for verification
Precision

Sometimes called:
- Reproducibility
- Replicate study
- Repeat results
- Repeatability

Defined as:

“The statistical closeness of agreement between repeated test procedures of the same sample under stipulated conditions.”\(^1\)
Precision

- Minimum of twenty (20) replicates, preferably over multiple days
- Can be performed on patient(s), known sample (i.e. duplicate QC or repeat calibration materials) over time
- Calculate the mean, standard deviation

Mathematical equations are available in the referenced CLSI documents.
Accuracy

Sometimes called:
- Correlation
- Method comparison
- Split sample
- Trueness
- Comparison to reference method
- Reference Lab Correlation

Defined as:
“The statistical closeness of agreement between a measured value and the true value.”
Accuracy

- Minimum twenty (20) samples, preferably over the entire analytical range and over several days
- Perform both tests on each sample
- Calculate correlation coefficient (coefficient of variation or CV or “r”)

*Mathematical equations are available in the referenced CLSI documents.*
Accuracy

A *linear* relationship is the goal:

- But where the line crosses the “x” axis is important, too!
Reportable Range

Sometimes called:
- Linearity
- Analytical Range
- Measuring Interval
- AMR, or Analytical Measurement Range
- AMI, or Analytical Measurement Interval

Defined as:

“The range of analyte values that a test method can directly measure on a sample without any dilution.”

\(^2\)
Reportable Range

- Sample size may be smaller
- Can use “spiked” samples
- Can use high and low calibration materials, or controls (or specimens)
- Can use a purchased linearity kit (e.g. College of American Pathologists)
Reportable Range

- Note: if dilutions are used beyond the linear limit, they should be validated.
- Mathematical equations for all applications are available in the referenced CLSI documents\(^1,2\) as well as the Westgard book/website\(^6\).
- For quantitative tests, a lab cannot use the reportable range established by a manufacturer if the entire range cannot be verified.
Reportable Range

Example:
The manufacturer's published reportable range is 1-100 ng/mL
The Laboratory verified the range from 5-90 ng/mL

Therefore:
The Lab’s reportable range becomes 5-90 ng/mL, and they cannot report patient values below 5 or above 90 ng/mL.
Reference Range

- If a full reference range study is not conducted, the manufacturer’s or published reference range must still be confirmed.
- Minimum twenty (20) samples
- Samples must be representative of the demographic characteristics of the Lab’s population.
Reference Range

- Reference range confirmations may be performed over time, concurrently with patient testing, while temporarily using the published reference range.

- Calculate mean, standard deviation and determine if +/- 2 SD is the appropriate reference range. If > 2 results (i.e. 10%) are out of range, the study must be repeated, and a new range implemented.
When is “PARR” Not Enough?

...If there is any modification from the package insert or manufacturer’s instructions.

(Then additional studies such as analytical sensitivity, specificity etc. are required.)
Some examples of “modifications” include:

- Use of a different specimen
  - e.g. using urine instead of plasma when urine is not stated on the package insert;
  - changing tube types- e.g. using PST tubes
- Changes in times, temperatures or dilutions- “tweaks”
- Changes or deletion of steps – “shortcuts”
- Change in the calibrator/ calibrator set points
- “Home-grown” tests
Validation/Verification Plans

- Some laboratories prefer a generic validation plan, with places to fill in the analyte, etc.
- Include a current package insert with your documentation.
- Some laboratories also prefer a generic validation summary form, in which the data can be written.
- Regardless, all must be signed by the CLIA Lab Director, prior to the initiation of studies. The CLIA Lab Director may decide to enhance these studies and/or increase sample sizes at any time.
Validation Plans

- **Best practices**: 
  - Include the complete, signed technical procedure
  - Define the type of quality control (QC)
  - Define Proficiency Testing or Alternative Assessment of Performance (AAP)
  - Define staff training and competency assessment requirements
Validation Plans

- Reference the instrument manual (if applicable) and/or other literature citations.
- Additional elements to consider include carryover and stability.
- Retrospective validations may be performed when no prior validation exists.
Validation Summary

- A summary document should be created which reviews the “PARR” data
- At the end of the document there should be a statement, “The above data has been reviewed, and this method is approved for patient testing”
- This must be signed & dated by the CLIA Lab Director prior to initiating patient testing.
References


References

5. The Joint Commission for the Accreditation of Healthcare Organizations; 2012 Laboratory E-dition

www.westgard.com
Questions?
Now, we are going to put your new skills to work...