Recommendations for Verification of Assays Performance - including Point of Care.

Verification is "provision of objective evidence that a given item fulfils specified requirements" (1)

ISO 15189 states: "The independent verification by the laboratory shall confirm, through obtaining objective evidence … that the performance claims for the examination procedure have been met." and "The performance claims for the examination procedure confirmed during the verification process shall be those relevant to the intended use of examination results." (2)

Verification studies are to demonstrate that the assay works in that laboratories hands the way the manufacturer intended following the manufacturers' Instructions For Use (IFU).

What assays are applicable for this document.

1. Assays performed on
    a. automated clinical biochemistry instrumentation,
    b. point of care instrumentation including hand held and small benchtop analysers,
    c. routine haematology cell counters
    d. analytical instrumentation to perform routine haemostasis (coagulation) studies.
2. In routine clinical biochemistry there should be no differences in the undertaking of verification studies whether wet or dry chemistry is used.

Use of a Verification Matrix.
It may be helpful for laboratories to use a verification matrix as outlined below to determine what verification actions are required.

Verification Matix

TEST METHOD	PLATFORM/INSTRUMENT				
	NEW TO MARKET*	NEW TO YOU	UPGRADE OF EXISTING	EXISTING IN YOUR FLEET	BUSINESS AS USUAL
NEW TO MARKET*	FULL + MAX TEST NUMBERS	FULL + MAX TEST NUMBERS	FULL + MAX TEST NUMBERS	FULL + MAX TEST NUMBERS	
NEW TO YOU	FULL + MAX TEST NUMBERS	FULL + MAX TEST NUMBERS	FULL Max Test No.s	MID MID range test No.s	
REFORMULATION	FULL + MAX TEST NUMBERS	FULL LARGE test No.s	MID LARGE test No.s	SLIM MID range test No.s	
EXISTING TEST	FULL + MAX TEST NUMBERS	MID Large Numbers	MID MID range test No.s	SLIM MIN TEST NUMBERS	
BUSINESS AS USUAL					REGULAR REASSESSMENT

DEFINITIONS	
FULL+	**FULL VALIDATION including linearity interferences etc et *Must be assessed to TGA/ARTG listing requirements***
FULL	Comprehensive Verification including linearity, lipaemia/haemolysis/icterus but not interfering compounds etc to NPAAC NATA requirements and in house IVD levels
MID	Patient Comparison regression analysis and Bland Altman Standard assessment per spreadsheet developed by NSW Health Pathology – available on request.
SLIM	Minimal comparison to show new location is operational

	Imprecision	Estimate MU	Patient Comparison*	HIL interference#	Other interference#	Linearity	Recovery	LoB, LoD, LoQ	Stability	Specimen type	Reference Interval
FULL+ (This is validation only)	20x2x2	+	120	+	+	+	+	+	+	+	Establish
FULL	5x5	+	40	+	+/-	+/-	+/-	+/-			Verify
MID	5x4	+	20								+/-verify
SLIM	5x2	+	10								

*Native patient samples are the preferred samples to use when undertaking method comparison studies. If native samples are not available due to analyte stability or other reasons then surrogate samples or QAP material may be used. Readers are referred to CLSI EP39 A Hierarchical Approach to Selecting Surrogate Samples for the Evaluation of In Vitro Medical Laboratory Tests.
#Additional studies (haemolysis or carryover etc) may be indicated and should be completed if required.

The verification study should reference an appropriate validations study.
For some analytes it may be important to characterise the limit of quantitation (LoQ). eg, cardiac troponin

Ideally, if quality control samples are used for the imprecision verification study, they should be different to the quality control material used to control the assay over the period of the study.

5x4 means four replicates per day over five days for each level.
5x 2 means two replicates per day over 5 days for each level

The assessment of agreement between methods in the analysis of patient comparison studies should use a Bland-Altman style difference plot or relative difference plot with calculation of the 95% limits of agreement and comparison to the analytical performance specifications. Regression analysis may also be performed using the method of Passing-Bablok (if N is 20 or greater), weighted Deming (if CV over the analytical measuring range is approximately constant), or Deming (if SD over the analytical measuring range is approximately constant). Simple linear regression may also be used if the coefficient of determination (r^2) is > 0.95.

Minimum Verification Requirements (1-5):

1. Imprecision
    a. QC samples should be run a minimum of 20 times and if possible a number of RCPAQAP samples should also be run. The QAP samples could be included in the 20 samples.
        i. These samples should be analysed over 5 days (ie 5 x 4)
    b. Results should undertake statistical analysis.
    c. For POCT devices a minimum of 10 samples should be assayed (ie 5 x 2)
    d. The imprecision results should be verified by the central laboratory ideally on day's 1 and 5.
2. Measurement of Uncertainty (MU)
    a. From the Imprecision data initial MU could be calculated if required.
3. Comparative study including bias (or trueness) analysis
    a. A patient comparisons study should be run and compared with results from the supervising lab or existing local lab platform. The number of samples will be determined by the Verification Matrix.
    b. These samples should include samples that challenge both the upper and lower critical limits of the test being performed.
    c. For POCT devices a minimum of 10 samples should be assayed
4. Reference Interval (RI) Verification
    a. From the comparative study data the RI validity could be determined if required.
5. Limit of quantitation (LoQ) of some assays, such as cardiac troponin should be undertaken by doubling dilution of a known sample following the guidelines suggested by Armbruster and Pry (5)
6. The verification study should reference an appropriate validations study.

Acknowledgements

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References:

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