UC Davis Health
Sacramento, CA
Department of Pathology and Laboratory Medicine

METHOD EVALUATION **Administrative Procedure 720.A**

PURPOSE:

To establish a uniform process of method selection and validation/verification for each test/method/instrument system before its use in patient testing. Each new or changed laboratory procedure needs to be validated by trial practice to ensure it works as expected and meets customer's needs. It is meant to be a guideline and help the laboratory meet applicable CAP/CLIA regulatory requirements.

SCOPE:

This procedure includes processes for:

- Selection, acquisition and identification of new equipment
- Installation and validation of new equipment
- Validation of new or changed test methods
- Re-qualification/Verification of existing test systems

DEFINITIONS:

Test System – The process that includes pre-analytic, analytic, and post-analytic steps used to produce a test result or set of results. A test system may be manual, automated, multi-channel or single-use and can include reagents, components, equipment or instruments required to produce results. A test system may encompass multiple identical analyzers or devices. Different test systems may be used for the same analyte.

Validation – Process of assessing the assay and its performance characteristics to determine the optimal conditions that will generate a reliable, reproducible and accurate result for the intended application. For non-FDA approved/cleared tests, the laboratory must establish the performance specifications.

Verification – Process performed to determine or confirm a test's expected performance compared to actual results produced by the laboratory. For tests cleared or approved by FDA, verification is required.

PROCEDURE:

I. The selection of a new or revised method and/or test platform is the responsibility of Laboratory managers, section supervisor(s) and section director(s)and must be approved by the Assistant Director and/or Pathology Director before acquiring, validating, and/or trialing any new instrumentation or methods. Method selection should start with a clinical perspective to ensure sufficient analytical reproducibility and accuracy to meet the clinical requirements and other considerations such as space, equipment and personnel, efficiency, turn-around time and cost effectiveness.

II. Selection Qualification(SQ) - Process for qualifying suppliers, making selection decisions and acquiring the equipment necessary for the provision of laboratory services. SQ process consists of the following four parts:

a. Identification of the necessary functional specifications and facility, environmental and engineering requirements for each piece of equipment the laboratory desires to acquire.
b. Comparison of needs to suppliers' functional specifications, capabilities and requirements offerings
c. Process for assessing and comparing acquisition alternatives, such as purchase, lease and rent.
d. Recording specifications, requirements, comparisons, decisions made, justification for the ultimate selection and follow up actions taken.

III. Equipment Acquisition and Identification – After equipment is acquired and received, it needs to be uniquely labeled or identified to enable traceability for all activities related to that piece of equipment throughout its lifetime. The equipment make, model, serial number and facility identification need to be recorded.

IV. Test system evaluation begins with a written process validation plan approved by the department director or his or her designee (section director). The validation plan encompasses the processes needed to perform a method validation. The processes will ensure that the new or changed test system works as expected and meets the laboratory standards. Validation Plan: The process validation plan may include the following elements:

A. Administrative Elements

Item	Description	Example(s)
Title	Brief descriptive title	Evaluation of the XYZ Random Access chemistry system.
Background	Briefly describe the reason for the process	The XYZ is a new instrument that will decrease turn-around time for routine chemistry tests and will replace the existing ZZZ chemistry instrument
Scope	Briefly describe the scope of the plan	This plan will involve instrument installation and test qualification for the XYZ instrument
Impact	Describe the impact on other departments	Will the change affect: • Sample requirements • Normal ranges • Turn-around time • LIS & EMR • Billing codes Does the project involve the LIS and billing departments?
Timeline	Provide an estimated timeline for the project	The project will take 160 hours and project time in weeks.
Responsibilities	Document responsibilities for all aspects of the project	Identify the following: • Project leader • Validation plan developer • Equipment installer • Software installer • SOP developer

Item	Description	Example(s)
		• Trainer • Testing personnel Who will review and approve the plan and the results, etc?

B. Technical Elements

Item	Description
Installation Qualification	Process to confirm the equipment and its component were supplied as ordered and properly installed in the laboratory meeting environmental requirements established by manufacturer. Performed by manufacturer's service engineer.
Operational Qualification	Process to confirm the equipment is operational for its intended use and location. Performed by manufacturer's service engineer
Performance Qualification	Process to confirm the equipment will perform per specified needs. Performed by laboratory staff.

The technical elements are described below in more detail:

1. **Installation Qualification**

Installation qualification may include the following:

a. List all equipment needed for the particular process (in addition to the main instrument, identify peripheral equipment needed for the test process including bar code readers, printers, centrifuges, water filtration systems, etc.)

b. Verify that environmental conditions are suitable for equipment (e.g. electrical requirements, adequate space, temperature, venting)

b. Include the following information, if applicable, on the equipment list for the validation packet.
- Equipment name & model number
- Manufacturer name
- Serial number
- UC Property Number
- Manufacturer/vendor manual title and revision date
- Computer software version
- Service Contract information

d. Add new equipment to applicable equipment lists.

e. Verify and document acceptable completion of installation checks on hardware, software and peripheral devices.

2. **Operational Qualification**

Operational qualification at a minimum includes the following:

a. Refer to vendor information and recommendations and identify instrument adjustment, calibration, and maintenance requirements. Includes training of instrument operation and testing operational requirements and functional performance by ordering, loading and running of controls, calibrators and a few patient samples.

b. Write procedures for instrument
- Operation
- Calibration
- Quality Control
- Preventive maintenance

c. Set up preventive maintenance, calibration and quality control schedules

3. **Performance Specification**

Method performance specifications must be performed in the location where testing will be performed. *Performance specification may include the following items. Not all items are applicable to all tests. Performance specification records are available to clients and/or inspectors upon request. Lab may require clients to treat the information as confidential.*

a. **Accuracy/Bias (=Systematic Error)**

Demonstrate how close to the "true" value the new method can achieve and can be determined by various methods including, but not limited to:

- Assaying materials with assigned values
- Comparing results to an established comparative Verifying results from inter-laboratory survey samples
- Splitting samples with another laboratory using the similar method
- Clinical correlation
- Assure that CLSI guidelines are followed. Must have approval of director if not possible.

b. **Precision (= Random Error)**

Precision is reproducibility. The ability of the laboratory to duplicate results time after time on different days and with different operators. Precision may be assessed by repeat testing of samples with known results, QC samples, control material or other suitable material.
- Within run
- Run to run, if multiple runs per day are expected
- Day to day, assure that CLSI guidelines are followed

c. **Reportable Range**

Reportable Range is the range of values that a method can directly measure without any dilution or concentration while maintaining accuracy.

When applicable, verify the following:
- Linearity (Analytical Measurement Range)
- Analytical Sensitivity (Limit of detection)
- Functional Sensitivity
- Dilution protocol (Clinical Reportable Range)

d. **Reference Range**

The reference range is a set of values determined to occur in a healthy, non-diseased population. Note that the verification of reference ranges may not be applicable to all test methods.

When establishing the reference ranges that will be included on the test report:
- Check literature references
- Check the manufacturer's package insert
- Test the relevant patient population when applicable.

Re-evaluation of reference ranges occur under the following conditions:
- Introduction of a new analyte into the test repertoire
- Change of analytic methodology
- Change in patient population

If it is determined that the reference range is no longer appropriate for the patient population, corrective action must be taken.

e. **Diagnostic (Clinical) Specificity & Sensitivity**

Due to lack of quantitative data, qualitative specificity validation is addressed by Diagnostic Specificity which is the percentage of subjects without the target disease or condition whose test values are negative.

Specificity: True Neg/(False Pos + True Neg) X 100

Diagnostic Sensitivity is the percentage of subjects with the target disease or condition whose test values are positive.

Sensitivity: True Pos/(True Pos + False Neg) X 100

Sensitivity and specificity are characteristics of the test. The population does not affect the results.
Negative and positive predictive values are useful when considering the value of a test to a clinician. Unlike sensitivity and specificity, the PPV

and NPV are dependent on the population being tested and are influenced by the prevalence of the disease.

Negative Predictive Value(NPV) is the probability that a patient in a given population with a negative test result does not have the disease of interest

NPV: True Neg/ True Neg + False Neg

Positive Predictive Value(PPV) is the probability that a patient in a population with a positive test result has the disease of interest.

PPV: True Pos/ True Pos + False Pos

Refer to the manufacturer's information.

f. **Analytical Specificity & Sensitivity**

Analytical specificity refers to freedom from interferences. Interfering substances are chemicals, solutions, materials or substances that can affect test performance. Review literature and manufacturer inserts for information regarding specificity.

Analytical sensitivity refers to the smallest quantity of analyte that can be reproducibly distinguished from background levels. For quantitative methods this includes determining the Limit of Detection. Refer to literature and manufacturer's information regarding sensitivity.

g. **Carryover**

Sample carry-over may cause one high patient sample to affect the subsequent sample.

Carryover studies must be performed:

- At the time the instrument is initially evaluated
- Periodically, at the discretion of the laboratory director or after major maintenance where carryover may be affected

h. **Continuing Quality Control**

Establish and follow written quality control procedures or Individualized Quality Control Plan (IQCP) (if appropriate) to monitor and evaluate the ongoing quality of the testing process.

- Ensure the procedure describes testing and reporting
- Perform and document calibration (if applicable) a minimum of every 6 months.
- Perform and document QC at clinically relevant decision levels when possible.

- Perform and document remedial action taken.

i. **Training Plan**

Prepare a training plan and submit to the department director for approval. Include a copy of the training plan in the validation packet.

j. **Initial and Continuing Competency Verification**

- Document training and initial competency according to the training plan instructions.
- Set up a schedule for ongoing competency for staff

k. **Proficiency Testing**

Ensure that the laboratory is enrolled in an appropriate proficiency testing survey or acceptable alternative.

l. **SOP Readership**

- Assure that all necessary staff have read the relevant standard operating procedures prior to test implementation
- Include copy of the final version of the SOP in the validation packet.

Note: it is acceptable to use the manufacturer's product insert during initial validation. This product insert will be adapted to an in-house SOP before test implementation.

m. **Laboratory Report Check**

Ensure that the laboratory report generated by the LIS and EMR are correct. Attach copies of actual reports to the validation packet.

V. **Re-qualification/Verification**

Each laboratory section is responsible for determining that its performance specifications for each test system are not affected by the relocation of the laboratory or test system. Performance verification is necessary after repairs or replacement of critical components of an instrument or item of equipment. (See manufacturer's package insert regarding critical requirements such as set-up, limitations, environmental conditions, etc.)

The re-qualification/verification procedure will address the following performance specifications of the test system as applicable:

a. Accuracy
b. Precision
c. Reportable Range
d. Reference Range (Normal Values)

Records will be maintained for performance verification.

VI. **Intermittent Testing**

When tests are put back into production, the following must be met:

a. Method performance specifications are verified.
b. Proficiency testing or alternative assessment is performed within 30 days prior to restarting patient testing. If the proficiency test used is from CAP and a survey is not offered within required time, alternative PT may be performed, and the lab must participate in the next scheduled PT event.
c. Competency is to be assessed for analysts within 12 months prior to restarting testing.

VII. **Records**

Records of method evaluations are maintained by the Technical Sections.

VIII. **Validation Packet**

Once the method experiments are complete, summarize the results in a Method Validation/Verification Packet. Submit the completed validation packet to the director for signature before proceeding with testing.

a. State the purpose of the verification, what platform/method and the number of samples for each experiment.
b. Any discrepant results should be investigated and explained in the Summary. Test results that show sample problems such as contamination and degradation should not be used in the assessment but still listed with an explanation.
c. When parameters are just outside acceptance criteria, additional testing can be performed (add more samples to the study), but do not delete data.
d. If the results show poor performance, check the instrument set-up, reagents, and procedures. Perform corrective actions and repeat the entire validation/verification study.
e. The Summary should also contain a conclusion stating whether the study met the acceptance criteria or not and its suitability for use in the laboratory.

The Department of Pathology and Laboratory Medicine, Method Evaluation Protocol checklist is attached at the end of this policy.
When an item is not applicable, a comment can be entered to that effect.

Please see an attached example of validation plan template from a technical section below:

Validation Plan

Test System:
Test(s):
The validation plan encompasses the processes needed to perform a method validation. The processes will ensure that the new test system works as expected and meets the laboratory standards.

Administrative Elements:

Item	Description
Title:	
Background:	
Scope:	
Impact:	
Timeline (mm/dd/yy):	Start Date: Estimated Time to Completion: Test Notification Date: Test "Go-Live" Date
Responsibilities:	Test Performance: Chemistry Supervisor: Chemistry Specialists: Review of Validation plan: Review test system qualification:

Technical Elements:

Item	Description
Installation Qualification	Equipment needed:
Operational Qualification	Write and update operational procedures to include:
Performance Qualification	Technical performance data will be summarized on the Clinical Chemistry Excel template. Data will be analyzed

Item	Description
	using established statistical packages including but not limited to Excel and EP Evaluator. Specimen Type(s): Reference Method: Accuracy: • Minimum of forty patient samples (n=40) spanning the reportable range and across more than one reagent lot will be compared between the new test method versus an appropriate reference method. Additional samples may be needed to establish appropriate statistical power. • Modified (e.g., spiking), calibrators, or College of American Pathologist (CAP) proficiency testing (PT) samples may be used if it is not feasible to obtain specimens with extreme values. The use of modified specimens and/or PT material must be approved by the Section Director. • Paired mean (SD) bias will be reported, and the appropriate statistical comparison made using either the t-test for paired differences (2 instrument comparisons) or one-way analysis of variance (ANOVA) (comparing more than 2 instruments). As appropriate, medians (range) may be used if the data is not normally distributed. • Outliers will be reviewed to determine if specimen matrix or confounding clinical factors contributed to the erroneous result. These outliers should be noted and reviewed by the Section Director. Precision: • Quality control material will be used for precision studies. The number of quality control levels will be based on the performance of the test method. At minimum two levels should be tested, however, the number of levels should span the entire measurement range and at relevant clinical cutoffs. • Within run precision studies (n=20) will be performed. The results will be reviewed based on the test's methodology, clinical significance, and statistical variation at the level of each control. • Between day precision will be performed control studies covering at least 5 days. A minimum of four replicates are performed for each level for each day. • Percent coefficient of variation (CV) is reported to establish within run, and between day precision. Linearity: • The appropriate linearity material spanning the analytical measurement range (AMR) will be used. • A minimum of three measurements will be for each data

Item	Description
	point. • Least squares or Deming regression will be used for data analysis. Analytical Range: Reportable Range: Reference Range: Carryover: Interference Testing*: Limits of Detection / Quantitation*: Clinical Sensitivity / Specificity*: Proficiency Testing: Continuing Quality Control Training Plan: Laboratory Report Check: ***Note:** Optional parameter for FDA approved in vitro diagnostic tests. Required if validating a laboratory developed test (LDT).

Approved by: _____ Date: _____
xxxxx., xxxxx, MD
Section Director, Clinical Chemistry

REFERENCES:

- College of American Pathologists, All Common Checklist, Current Edition
- Clinical Laboratory and Standards Institute Laboratory (CLSI): *Instrument Implementation, Verification, and Maintenance*; Approved Guideline. GP31-A (ISBN 56238-697-2). Clinical Laboratory and Standards Institute, 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898 USA, 2009.

PROCEDURE HISTORY

Date	Written/Issued by	Revision/Annual Review	Approved Date	Approved by
6/85	E. Dixon	New	6/85	M. Gardner
2/92	E. Dixon	Revised	2/92	R. Cardiff
3/93	D. O'Sullivan	Revised	3/93	R. Cardiff
9/94	D. O'Sullivan	Revised	9/94	R. Cardiff
4/96	D. O'Sullivan	Annual Review	4/96	R. Cardiff
10/96	D. O'Sullivan	Annual Review	10/96	R. Green
12/97	D. O'Sullivan	Annual Review	1/98	R. Green
7/99	D. O'Sullivan	Annual Review	7/99	R. Green
6/00	D. O'Sullivan	Annual Review	6/00	R. Green
11/00	D. O'Sullivan	Revised	11/00	R. Green
10/01	D. O'Sullivan	Annual Review	10/01	R. Green
8/02	D. O'Sullivan	Annual Review	8/02	R. Green
10/02	B. Harris	Revised	10/02	R. Green
10/03	B. Harris	Annual Review	10/03	R. Green
11/04	B. Harris	Revised	11/04	R. Green
6/05	B. Harris	Revised	6/05	R. Green
9/06	K. Omand	Annual Review	9/06	R. Green
9/07	K. Omand	Annual Review	9/07	R. Green
7/08	D. Wright	Revised	7/08	R. Green

Date	Written/Issued by	Revision/Annual Review	Approved Date	Approved by
7/09	D. Wright	Annual Review	7/09	L. Howell
5/10	D. Wright	Revised	5/10	Dr. L. Howell
5/11	D. Wright	Annual Review	5/11	Dr. L. Howell
09/12	T. Cox	Revised: re-establish reference ranges; intermittent testing	09/12	L. Howell
09/14	T. Cox	Revised: added 30 days PT; reverification after instrument repair, relocation	09/14	L. Howell
09/16	S. Okimura	Revised: added IQCP and clerical corrections	09/16	L. Howell
06/17	N. Kaur/ S. Okimura	Revised: added process for selection, acquisition and identification of new equipment, added example validation plan template and reformat	06/17	L. Howell Via Onbase
05/19	N. Kaur	Revised: Position titles and Reference	05/19	L. Howell Via Onbase
04/21	E. Karanja	Revised: Added Addendum A to procedure, revised validation plan template	5/21	L.Howell Via OnBase

METHOD EVALUATION Addendum A **Administrative Procedure 720.A**

Analyte: _____ **Method/Instrument:** _____

Test Implementation Date: _____ **Cost Center:** _____

Please include the following items with approvals in the validation packet.		**Approval:**	
ITEM		**Dept.**	**Date**
PLAN			
	Approved Validation Plan		
INSTRUMENT			
	Installation Qualification for test Equipment		
	Operational Qualification for test Equipment		
	In-house Preventive Maintenance Schedule		
	Set up QC, limits, ranges, dilutions, calibration intervals, etc.		
VALIDATION TESTING RESULTS AND PARAMETERS			
	Accuracy		
	Precision		
	Linearity(Analytical) and Clinical Reportable Range		
	Sensitivity		
	Specificity		
	Hook effect		
	Carryover		
	Reference Range (if indicated)		
	Operating Parameters (if indicated)		
	List of Reagent & Calibrator Lots Used		
	SOPs used during validation testing		
	Product inserts used during validation and SDS sheets		
	Raw Data		
WRITTEN PROTOCOL			
	Final SOP		
QUALITY CONTROL			
	List Product		
	Establish Reporting method		
	Define ranges and enter ranges into instrument, LIS, QC book		
PROFICIENCY TESTING			
	List Program subscribed to		
TRAINING PLAN			
	Initial training plan and assessment		
COSTS & BILLING			
	Cost analysis		
	Supply agreements and service contracts		
	CDM creation and Billing code		
COMPUTER UPDATES & REPORTS			
	LIS changes (Submit Enhancement Request Form)		
	GATEWAY Website Test created/updated		
	Copies of 1st LIS and EMR report from 1st live run		
NOTIFICATIONS			
	Memo to Faculty & Housestaff as applicable		
	Notification to Laboratory Section Staff		

Director Sign-off on this validation study confirms that it has been reviewed and the performance of this method is considered acceptable for patient testing.

Section Director Sign Off	**AND/OR**	**Laboratory Director Sign Off**
Date		