Test Method Validation of In-Vitro Diagnostic Products

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IVD Overview
What is an In-Vitro Diagnostic Test

- IVDs are medical devices and accessories
- Used to perform tests on samples, (e.g., blood, urine, tissue) in order to:
  - Help detect infection
  - Diagnose a medical condition
  - Prevent disease
What is an In-Vitro Diagnostic Test

- Systems and tests used in clinical laboratories
- The tube of blood “sent to the lab”

Beckman Coulter
UniCel DxI 800 Access
What is an In-Vitro Diagnostic Test

- OTC tests for consumer use at home

The hCG Urine Pregnancy Test Strip is a test kit for the determination of hCG (Human Chorionic Gonadotropin) in urine specimens. This test kit is used to obtain a visual, qualitative result for the early detection of pregnancy.
Design Verification vs. Test Method Validation
Design Verification

- 21CFR 820.30(f) Design verification shall confirm that the design output meets the design input requirements.

- The goal of design verification is to provide the evidence that the Design input requirements are met by the product design.
Test Method Validation

- Test method validation is the documented process of ensuring a test method is suitable for its intended use.

- The goal of TMV is to provide the objective evidence that a test method will fulfill its intended use, such as releasing a lot of reagent for sale.
TMV of IVD Products
Topics

- Validation & Test Methods
- General TMV Flow
- Intended Use & Requirements
- Test Method Characterization
- Validation Sampling Plan & Acceptance Criteria
- Test Method Validation Protocol
- Re-Validation Assessment
What is a Test Method?

**Definition:**

A definitive procedure that measures a characteristic of material, product or equipment against defined acceptance criteria for that characteristic.
What is a Test Method?

Examples:

- **Visual Inspection** - raw material inspections using an acceptance sampling plan.
- **pH** - measure of the activity of the solvated hydrogen ion.
- **Particle mix test** - instrument final release, testing the ability of the sonication probe to adequately mix the particle well.
- **HPLC** (high pressure liquid chromatography) - in-process testing to determine the % purity of an antibody.
- **Value assignment** - Using an Access 2 or DxI to assign a value to a control or patient.
- **Functional test** - Using an Access 2 or DxI as release testing for reagent packs for sale to customers.
Test Method Types

- **Attribute**: Data to be evaluated is qualitative (for example, pass/fail)

- **Variable**: Data to be evaluated is quantitative (for example, a measured value).
  - **Analytical**: is a subset of a variable test that evaluates an analyte for accuracy, precision, specificity, detection limit, quantitative limit, linearity or range data.
What is Validation?

- **Confirmation by examination and provision of objective evidence that the particular requirements for a specific intended use can be consistently fulfilled**
What is Validation?

The validation of the test method establishes that:

- Characteristics of the test method meet the requirements for its application
- Test method is fit for its intended use
- Results are consistent and repeatable
TMV Big Picture

Plan

Test Method

Validation

ESTABLISH THE OBJECTIVE
Define intended use
Specify requirements

CHARACTERIZATION
Get data or generate new data
Identify variance components (factors)
Generate an MSA

GENERATE THE TMV PROTOCOL
Classify validation type
Identify risk and variance components (factors)
Establish acceptance criteria

EXECUTE THE TMV PROTOCOL
Perform testing according to the MSA

ANALYSIS
Analyze the data
Interpret the results against the acceptance criteria

GENERATE THE TMV FINAL REPORT
Report the results with discussion as appropriate

Implement the validated test method
TMV Planning

- Intended Use and Requirements
- Characterization/Engineering Studies
- Risk Analysis
- IOQ for Test Equipment
- TM Procedure
Intended Use

- In test method validation, intended use refers to the application of the test method.
  - Quantify a “Quality Attribute”
  - Value assign control material
  - To make a product disposition decision
- It does not refer to the intended use of the product on test.
Intended Use

- Where & When Used and for What?
- How does it work?
- What does it measure/determine?
Requirements

- **Definition:**
  - The requirements of a test method are defined in terms of performance characteristics that must be met in order to achieve the intended use.

- **Note:**
  - This does not refer directly to customer requirements for the product on test. However, the customer requirements or claims may dictate the requirements of the test method.
Requirements

• What am I measuring?
  ▶ Analytical performance characteristics
    Specificity/ Selectivity    Linearity
    Range                      Accuracy
    Precision (required)       Detection Limit
    Quantitation Limit         Stability

• How good does the measurement have to be?
## IMAT System Check

<table>
<thead>
<tr>
<th>Sample Size</th>
<th>Accuracy Requirement</th>
<th>Precision Requirement</th>
</tr>
</thead>
</table>
| 20          | Sample will be measured against the requirements for System Check test (see table below)  
              (See Table 4 BCP0051-Appendix for 2 Sided sampling plan) | Cpk of RLU Mean for all tests ≥ 0.81  
              Cp of %CV for all tests ≥ 0.87 |
Validation Acceptance Criteria

- Validation Acceptance Criteria **Is** -
  - The criteria used to evaluate the test method
    - based on severity of risk for the failure modes

- Validation Acceptance Criteria **is Not**:  
  - specifications for the product or process  
  - used to evaluate the product or process
Validation Acceptance Criteria

- Each Requirement must have an acceptance criteria
  - Estimated/Established during MSA
    - Precision
      - Cpk, %CV, Test Method Standard Error
      - Consult with Biostatistician
    - Precision (non-analytical)
      - Statistical Techniques for Process Validation
        - Ppk, Cpk
Test Method Characterization

Understand the variability inherent in the test method

▲ Why?
   ➢ To confirm that variation is not excessive or to take action if it is excessive
   ➢ To set validation acceptance criteria
   ➢ To set TM sample plans

▲ How?
   ➢ MSA/Gage R&R
   ➢ Product Variability Analysis (PVA)
Legacy Product

- Historic data is used for characterization and establishing test methods
- Must meet predefined acceptance criteria
New Product

- Historic data limited, characterization (PVA 1 using dev lots) establishes the test method (minimum sample plan)
- Pilot PVA (PVA 2) executed as the validation, sample plan adjustments can be made (increased sample plan)
Validation Strategy

New Product Development

- Use PVA 1 to establish sample plan based on product specification, variance components and suggested $C_p \geq 1.33$
- Execute validation to generate PVA 2
- Verify test method variability using PVA 2 data
- If differences between PVA 1 and PVA 2, investigate
- Sample plan may be increased with rationale
Validation Strategy

Value Assignment Test Method
Determine the acceptance criteria based on the expected Cl% width.

Example
- Specification: ± 10% of target
- Acceptance criteria: ± 5% of target (95% Cl)
Validation Strategy

Value Assignment Test Method

Example

- Specification: ±8%
- Manufacturing Process Uncertainty: 3.32%
- Acceptance criteria: 4.68% (95% CI)
Analytical TM Characterization

- Procedures
- Gages & Equipment
- Product Being Measured
- People
- Environment
- Measurement System
- Measurements
Analytical TM Characterization

Variability Analysis (MSA, Gage R&R)

- What’s your data?
- Where’s your data?
- Can you get the data?
- May have to generate data

* List all potential factors from your historical data.
  * Day-to-day
  * Operator-to-operator
  * Instrument-to-instrument
  * Run-to-run
  * Rep-to-rep
  * Lot-to-lot
  * Shift-to-shift

* Carry out additional experiment(s) to capture factors of interest:
  * Confounding factors
  * Factors not captured in historical data
Analytical TM Characterization

Variability Analysis

<table>
<thead>
<tr>
<th>Variance % of Total</th>
<th>Prefill Ctrl 1</th>
<th>Prefill Ctrl 2</th>
<th>Prefill P01</th>
<th>Prefill P02</th>
</tr>
</thead>
<tbody>
<tr>
<td>INSTRUMENTNUM</td>
<td>27.45</td>
<td>0.00</td>
<td>10.82</td>
<td>39.99</td>
</tr>
<tr>
<td>ASSAYKEY</td>
<td>0.00</td>
<td>8.31</td>
<td>0.00</td>
<td>31.17</td>
</tr>
<tr>
<td>REPLICATENUM</td>
<td>72.31</td>
<td>91.69</td>
<td>89.18</td>
<td>28.85</td>
</tr>
<tr>
<td>Day</td>
<td>0.24</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>
Test Method

- Specification
- Risk Analysis
  - Severity/Impact for failure
  - Confidence and Power levels
  - Characterization
    - Variability
    - Variance components
- Test Method Sampling Plan
TMV Big Picture

- **Plan**
  - Establish the Objective
    - Define intended use
    - Specify requirements
  - Characterization
    - Get data or generate new data
    - Identify variance components (factors)
    - Generate an MSA
  - Generate the TMV Protocol
    - Classify validation type
    - Identify risk and variance components (factors)
    - Establish acceptance criteria

- **Do**
  - Execute the TMV Protocol
    - Perform testing according to the MSA
  - Analysis
    - Analyze the data
    - Interpret the results against the acceptance criteria
  - Generate the TMV Final Report
    - Report the results with discussion as appropriate

- **Test Method Validation**
  - Implement the validated test method
After TMV...

- **TMV Revalidation**
  - Method parameters change
  - New compounds are analyzed that are not within the method’s original scope
  - Equipment, specifications change

- Assess to determine impact, may require revalidation.
Re-Validation

Any change to a validated process that has the potential to affect the process output must be considered for re-validation. This includes, but is not limited to, changes to raw materials, processing equipment, processing parameters, process location, process specifications, or test methods.
After TMV...

How is validation impact assessed?

- Re-Validation Assessment Form:
  A document used to evaluate the impact a change may have to a previously validated process or test method and to document the validation activity required as a result.
### Assay TMV Example

**Assay reagent pack prefill functional testing:** The ability of the reagent pack test method to consistently measure sample on test.

<table>
<thead>
<tr>
<th>Analytical Performance Characteristic</th>
<th>Requirement</th>
<th>Acceptance Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Precision</td>
<td>Repeatability: within assay variability and increasing the sampling of each replication Reproducibility: assay to assay, instrument to instrument and day to day variability and increasing the sampling of each factor as necessary.</td>
<td>Achieved TMSE ≤ Estimated TMSE Test Method Standard Error (TMSE)</td>
</tr>
</tbody>
</table>
# Real Time Stability TMV

<table>
<thead>
<tr>
<th>Requirement Type</th>
<th>Requirement</th>
<th>Acceptance Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accuracy of the stability test result (Linear Regression)</td>
<td>At a minimum of three time points:</td>
<td>Stable Product: The test method detects when there is no relationship between percent difference and time:</td>
</tr>
<tr>
<td></td>
<td>• The test method detects when there is no relationship between percent difference and time (i.e. stable product).</td>
<td>• the p-value of the regression fit for each plot is not significant ($p&gt;0.05$) or the p value is significant ($p \leq 0.05$) and</td>
</tr>
<tr>
<td></td>
<td>At a minimum of three time points:</td>
<td>• the confidence interval does not intersect the analyte specific tolerance limit.</td>
</tr>
<tr>
<td></td>
<td>• The test method detects when there is a relationship between percent difference and time (i.e. unstable product)</td>
<td>Unstable Product: The test method detects when there is a relationship between percent difference and time:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• the p-value of the regression fit for one plot is significant ($p \leq 0.05$) and</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• the confidence interval does intersect the analyte specific tolerance limit.</td>
</tr>
</tbody>
</table>