Validating Methods using Waters Empower™ 2
Method Validation Manager (MVM)

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1. Method Screening / Optimization
   - Mining data, summarizing and selecting decision-centric method development information workflow
   - Analyst team combines data from collaborating scientists to produce reports with recommendations or feedback for further experiments

2. Impurity Profiling:
   - Orthogonal data to assist specificity
   - Build experiment sample list
   - Method search for existing conditions or published papers

3. Method Validation: Linearity, Accuracy, Precision
   - Author final experimental write-up/report with results & information using the SDMS authoring tool and templates

Review and select best options of reports/summary’s captured from each step. Move information seamlessly into SDMS VP as a parallel workflow

Capture and catalog:
- Original file
- Project data
- Printed report
- Meta data

Printed e-reports captured and cataloged from analysis in NuGenesis SDMS

Decision-centered method development information workflow
MVM Background

- MVM: the result of a significant R&D effort with collaboration with several big pharma
- Goals of the MVM project
  - Time savings of the method validation process
  - Elimination of the error prone aspects of the process
  - Compliance
  - Confidence in results

Why Validate?

- Regulatory Compliance
- Method validation provides assurance of reliability

"The process by which it is established, by laboratory studies, that the performance characteristics of the analytical method meet the requirements for the intended analytical applications."

“…to demonstrate that the method is suitable for it's intended purpose.”

References:
US. Pharmacopeia, Chapter 1225
ICH Q2(R1)
Example Tests

Linearity

Precision vs. Accuracy

Analytical Method Validation Process

Time consuming, repetitive tasks consisting of several sequential steps
**Problems with Manual Process**

- Constant referral to paper SOP
- Multiple data transfer steps to multiple software applications
  - Error prone process
  - Additional validation requirements for additional software applications
  - Additional data checking required to prevent transcription errors
  - No automatic traceability of validation data back to chromatographic data
- Security and compliance concerns
- No consistency in final reports
- Manual and error prone data tracking, documentation and mining from protocol to final reporting
- Lack of confidence in result integrity

**With Method Validation Manager**

You can automatically...

- Perform and manage entire method validation workflow in Empower 2
  - Eliminate compliance concerns
  - Automatic traceability of data and meta data
  - Empower understands your validation requirements
- Create efficient sample sets
  - Reuse injections for multiple validation tests
- Monitor what step in the process you are at
  - MVM tells you what you need to do next
- Perform all results and statistical calculations in Empower 2
  - No additional software or spreadsheets required
  - Eliminate transcription errors
- Automatically determine if your results are out of specification
  - Easily find responsible data, troubleshoot and rectify problem
- Realize time savings of up to 80%
Steps in the Validation Process

- Administration and configuration
- Navigating the validation workflow
- Data review and troubleshooting
- Final Reporting
- Summary
Validation Tests

Corporate Validation Requirements translated into a (generic) Validation Protocol Method(s) in Empower 2

Phased Approach: Requirements depend on Compound Type, Method Type, and Development Phase

- Specificity
- Linearity
- Linearity Comparison
- Accuracy
- Repeatability
- Intermediate Precision
- Reproducibility
- Robustness
- LOD
- LOQ
- Filter Validation
- Stability
- System Precision

Transfer Paper SOP to Empower Validation Method

The elements of the written validation protocol are transferred into the MVM validation protocol method format: a one-time activity

Add appropriate validation tests to table

Configure each validation test
Specify details about the data that should be acquired

“The ICH documents recommend that accuracy should be assessed using a minimum of nine determinations over a minimum of three concentration levels, covering the specified range (i.e. three concentrations and three replicates of each concentration).” (USP)

“The specified range for assay of a drug substance: 80% to 120% of the test concentration” (USP)

Specify the acceptance criterion for your results

Accuracy is calculated as the percentage of recovery by the assay. (USP)

% Recovery should be within the range 95% to 105%

Acceptance Criteria set for
• the mean at each concentration level
• Individual injections
Sample set methods (generic) are created to optimize the efficiency of data acquisition. Within the sample table, select the validation test to which each injection pertains.

<table>
<thead>
<tr>
<th>No</th>
<th>Vol</th>
<th>Sample Name</th>
<th>Inj Vol (µL)</th>
<th>Method Set / Report Method</th>
<th>Run Time (Minutes)</th>
<th>Level</th>
<th>System Precision</th>
<th>Linearity</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Blank</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Test injection</td>
<td>100%</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>A/F-80%</td>
<td>80%</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>A/F-100%</td>
<td>100%</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>A/F-120%</td>
<td>120%</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Allows multiple validation tests to be performed in one sample set
- Allows injections to be ‘reused’ for multiple validation tests
- Allows data from another CDS to be used in a method validation study (edit the sample data after importing it into Empower)
- Allows Empower 2 to manage and check the entire validation data
- The analyst need only concentrate on matching the dictated sample set format with the appropriate samples and vials

### Addressing Complex and Time-Consuming Validation Tests

**Robustness:** The measure of its capacity to remain unaffected by small, but deliberate variations in method parameters. Provides an indication of the method’s reliability during normal usage.

- Determines the sensitivity of the tested method parameters to small, purposeful variations.
- The most time-consuming validation test.
- A parameter that fails robustness criteria will need to be tightly controlled when routinely performing the assay.
- 2 approaches: vary one-parameter-at-a-time vs. vary multiple parameters at once. Governmental guidelines do not advocate one approach over the other.
- Latter approach allows for more efficient data acquisition and a comprehensive statistical result analysis, including information regarding factor interactions.
MVM provides a flexible and statistically comprehensive approach to robustness testing.

MVM uses Design of Experiment (DOE) to dictate statistically appropriate experiments to the user.

The user simply specifies the factors they want to analyze and the Experiment Design Type; MVM then designs the necessary experiments for you.

The necessary experiments (injections) are displayed to the user in a table that can be pasted directly into the sample set.
The elements of the written validation protocol are transferred into the MVM validation protocol method format: a one-time activity.

Add appropriate validation tests to table

Configure each validation test
Steps in the Validation Process

- Administration and configuration
- Navigating the validation workflow
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Validation Workflow
## Validation Workflow

**Test Status**

Indicates what step you are at in the workflow.

### Validation Manager

**Automatic Data Checks** ensure the correct number of data points, levels, etc.

**Data status fields** indicate whether your data passes your validation protocol requirements.

- **OK**
- **Not OK**
- **OOS** (out of spec)
- **OR** (over ridden)
Error messages in the Message Center effectively guide all troubleshooting activity.

The number of injections per visit does not match the number specified in the System Precision configuration parameters.

MVM ensures that all sample sets contain injections match their respective test configurations.

When data does not meet your requirements, the Message Center provides specific information regarding the problem.

Validation Workflow

Results are processed in seconds with one button click.

Data is quickly processed and validation result status indicates Pass or Out of Specification (OOS).
Interpreting Results

- Navigation Tree
- Results are unique to each validation test
- Plots and tables available for each validation test type
- Data within plots and tables are interactive
- OOS data is highlighted and “faulted”

Interpreting Results - Linearity

Important results include:
- Equation of the line
- R and R²
- Residuals
- Response Factors
- Y Intercept % Bias

Linearity Plot and Residuals Plot
**Interpreting Results- Accuracy**

Accuracy Plot: % Recovery is displayed for each data point, for each concentration level, and for the entire data set; User-defined acceptance criteria is indicated by ‘whiskers’ in the plot.

Important results include:
- % Recovery
- Average % Recovery
- Standard Deviation
- % RSD
- Confidence Interval
- ANOVA Statistics

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**Interpreting Results- Robustness**

Effects Plot

Effect = the change in response due to the change of a factor.

Important results include:
- Effect of factors and factor interactions
- Variance of factors and factor interactions
- ANOVA statistics
**Interpreting Results - Stability**

Stability Plot: Stability allows assessment of samples over time at different storage conditions; each time point is compared to the T=0 reference data.

Important results (at each time point and storage condition) include:
- Assessed field value
- Average
- Standard Deviation
- % RSD
- Confidence Interval
- ANOVA Statistics
- Degradation rate
- Relative Area % (Relative to Active Ingredient)

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**Steps in the Validation Process**

- Administration and configuration
- Navigating the validation workflow
- Data review and troubleshooting
- Final Reporting
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Streamlined Data Review

Supervision/ Review

- Normally – Review involves a pile of chromatograms and tables from the CDS and spreadsheets, possible transcribed manual calculations, and a lot of time.

- With MVM – Out of Specification results are automatically flagged. Navigation to outlying data points is easy with the interactive review of result in plot and tabular format.

Data Review – Out Of Specification (OOS) Result

The status of final results for each of the validation tests are clearly displayed in the validation manager window.

Acceptable results

Out of Specification results
OOS Results Flagged in Validation Review

- Whiskers on plot indicate acceptance criteria
- Trend plot gives overview of individual data points
- Failed results are bold red

Easily Trace OOS Results to the Original Chromatographic Data

The 'failed' chromatographic injection is easily found
OOS Results Flagged on Reports

Data Review: Approvals and Electronic Sign Offs

Approvals and sign offs provide optional checks in the workflow.
Steps in the Validation Process

- Administration and configuration
- Navigating the validation workflow
- Data review and troubleshooting
- Final Reporting
- Summary

Automated Report Generation
Method Validation Manager Reports Captured and Stored within NuGenesis SDMS

Linearity Plot Retrieved from NuGenesis SDMS and highlighted within Vision Publisher Final Report
The value of electronic information management

How can this help your laboratory’s make better and faster decisions?

- **Documenting decision making on test results**
  - Reduce time spent managing paper reports
  - Automate review and sign-off processes
  - Generating faster response during regulatory inspections
  - Speeding up and automating the hand-over to manufacturing

- **Share, collaborate and partnership across the globe**
  - Improve the ability to search, access and efficient use all content generated
  - Solve data duplication of analysis
  - Optimize available resources

- **Regulatory compliance**
  - Document traceability for increased confidence
  - Facilitate and protect intellectual property
Analytical Method Validation Process with Method Validation Manager

- Prepare Standards & Samples
- Create Sample Sequence
- Data Acquisition & Processing
- Calculation
- Statistical Results
- Reports Compiled
- Data Management

Faster and Easier Method Validation

Perform Method Validation Faster and Easier...

- Manage entire method validation workflow in one comprehensive, automated application
  - Eliminate time consuming data transfer between multiple software applications and associated transcription errors, security concerns and validation requirements
  - Perform all (structurally validated) results and statistical calculations in Empower 2
  - Clearly display the status of on-going validation studies
  - Process validation results with a click of a button
  - Straightforward data viewing and interpretation
  - Ease of data review and acceptance
- Entire process is less error prone
- Up to 80% time savings
MVM Case Study

A scientist with the company’s global R&D division indicated that nonsample prep activities account for approximately 60 percent of the time consumed in a method validation study. With Empower 2 MVM, he estimates this could be reduced to as little as 10 percent, representing a 50 percent overall time-savings (see Table 1). Just as importantly, the scientist said with Empower 2 MVM, he is more confident that his method validation data is accurate and traceable.

<table>
<thead>
<tr>
<th>Validation task</th>
<th>% of Total validation time</th>
<th>Time-savings with Empower 2 MVM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Administrative</td>
<td>20</td>
<td>75</td>
</tr>
<tr>
<td>Sample Prep</td>
<td>40</td>
<td>0</td>
</tr>
<tr>
<td>Processing Data</td>
<td>20</td>
<td>95</td>
</tr>
<tr>
<td>Report Generation</td>
<td>20</td>
<td>80</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
<td>50</td>
</tr>
</tbody>
</table>

Table 1. Method validation time-savings with Empower 2 Method Validation Manager.

Assure Regulatory Compliance

Empower 2: Compliant Ready Software

- All calculations done in Empower
  - Calculations are structurally validated
  - No additional software to manage
  - No spreadsheets of which to validate functions
  - Data is secure in the Empower database
  - Easily trace validation results back to the raw data
- Fully audit traced activities
- Full Set of User Privileges and access control for data security
Visit www.waters.com/MVM for more information