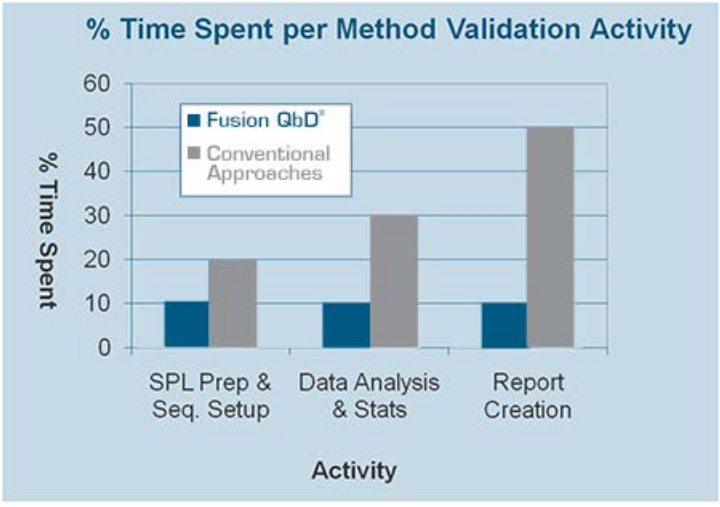
Fusion QbD® Software System

Fusion Analytical Method Validation

The Only Software That Has It All!

- **100% aligned with FDA/ICH Quality by Design (QbD) guidances!**
- **Can be used for LC and Non-LC methods (e.g. GC, CE, Q-NMR)!**
- **Automates LC method validation experiments on multiple instruments and CDS systems!**
- **Regulatory accepted validation for both Small & Large Molecules!**
- **Statistically rigorous and defensible robustness testing!**
- **Handles multiple compounds – creates complete reports for each!**



- **Shortens your LC method validation time by as much as 75%!**

Automated Experimentation for LC Method Validation

The objective of Method Validation is to provide documented evidence and a high degree of assurance that an analytical method employed for a specific test is suitable for its intended use. Method Validation is a regulatory requirement as much as a scientific necessity.

Key Benefits

- Full Automation for LC Method Validation – multiple LCs and CDS systems
- Phased Method Validation –
  - Early Phase – performance characterization supports development
  - Final Phase – Aligned with FDA and ICH guidances
- 21 CFR 11 compliance support toolset –
  - Including E-records and E-signatures, full audit logging
  - Workflow management system with E-review and E-approve loops
- Easy setup of experiments –
  - Create standardized workflow templates
  - Facilitate rigorous practice and defensibility
- Simple documentation review and reporting –
  - Easy to defend and communicate
  - Reports meet all FDA and ICH guidelines

Early Phase Method Validation (Performance Characterization)

Analytical Capability and System Suitability
Specificity
Filter Validation
Accuracy
Linearity and Range
LOQ, LOD
Repeatability* (intra-assay precision)
Sample Solution Stability (stability for a given time period under prescribed conditions)

Final Phase Method Validation (FDA and ICH Submittal Quality)

Analytical Capability and System Suitability
Specificity
Accuracy/Linearity and Range/Repeatability – Combined Design
[ICH-Q2(R1) – Accuracy, Linearity, and Repeatability can be done together as a single combined experiment]
LOQ, LOD
Intermediate Precision and Reproducibility (USP Ruggedness)
Robustness – done the right way!

Non-LC Method Validation Experiments

Used successfully for Non-LC methods such as GC, CE, Q-NMR, as well as hyphenated methods (e.g. LC-MS). Accepted in customer regulatory submittals.

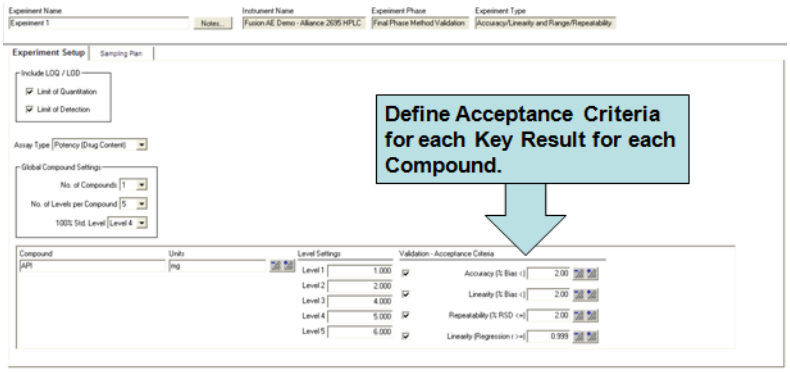
Automated LC Method Validation – Five Step Workflow

1. You complete a simple experiment setup template.
2. Fusion QbD creates the Validation Experimental Design and exports it to the CDS.
3. The CDS runs the validation experiment sequence.
4. Fusion QbD imports and analyzes the results.
5. Fusion QbD automatically creates final reports and graphs.

Example Workflow – Combined Accuracy / Linearity / Repeatability

Step 1 – You Complete the Template

Fusion LC Method Validation Software (FMV) has simple experiment setup templates for each type of validation experiment. The simple Linearity and Range template is shown below with user definable settings:



User-definable Settings – Basic Setup

- Include Limit of Quantitation
- Include Limit of Detection
- No. of Compounds
- No. of Levels per Compound
- 100% Standard Level
- No. of Injections of 100% Level

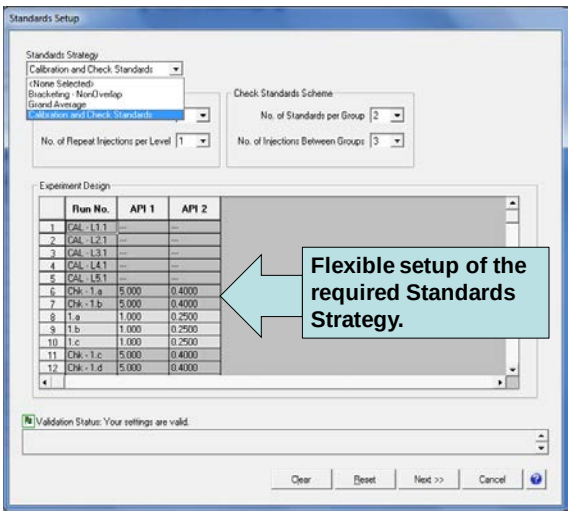
User-definable Settings – Method Performance Acceptance Criteria

- Linearity (% Bias <)
- Linearity (Regression r >=)
- Accuracy (% Bias <)
- Repeatability (% RSD <=)

User-definable Settings – Standards Setup

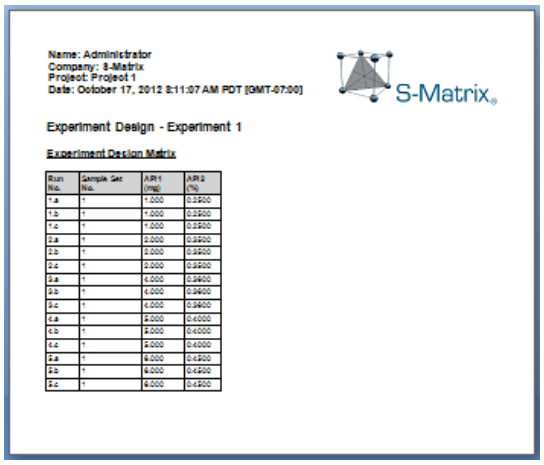
FMV has a flexible Standards Setup wizard which enables you to select your desired standards strategy for results quantitation within the CDS:

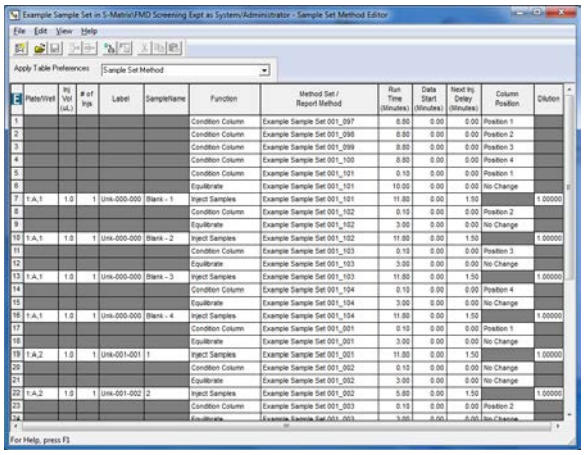
- Bracketing – Overlap
- Bracketing – Non-overlap
- Grand Average
- Calibration and Check Standards



Step 2 – Fusion QbD Creates the Validation Experimental Design and Exports it to the CDS

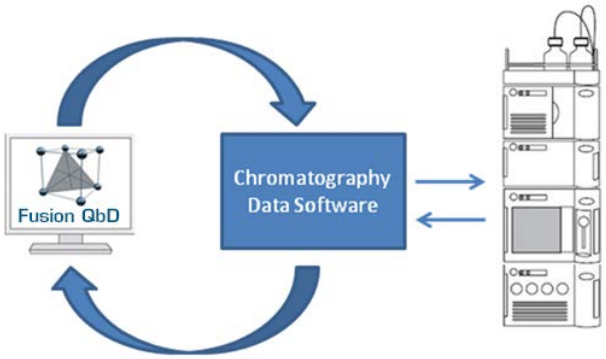
FMV automatically constructs the validation experiment designs within the CDS as ready-to-run sequences/sample with the proper Vial No. and Injection Type designations for Samples, Standards, and Blanks.





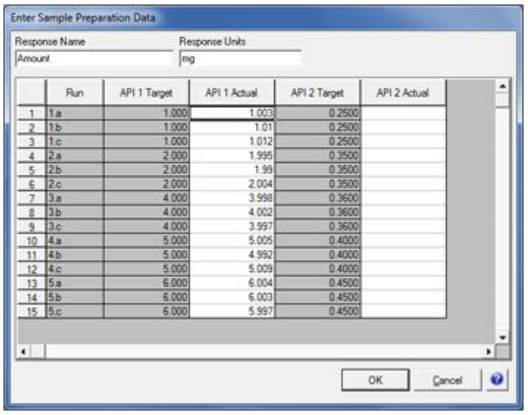
Step 3 – CDS runs the Validation Experiment

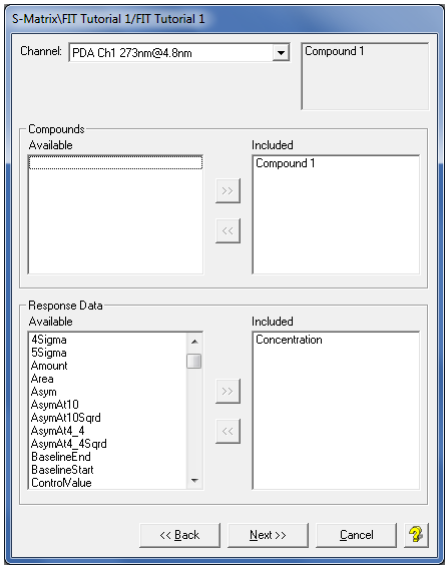
FMV sequences run automatically on the CDS. **FMV** even enables you to include a Shutdown method as the last method run so that you can execute **FMV** sequences overnight while you sleep!



Step 4 – Fusion QbD Imports and Analyzes the Chromatogram Results

FMV automatically imports the required peak result data from the CDS, and re-maps the results to the design for automated analysis, graphing, and reporting. This is a key feature ensuring quality, as manual transcription is a common source of error and risk.





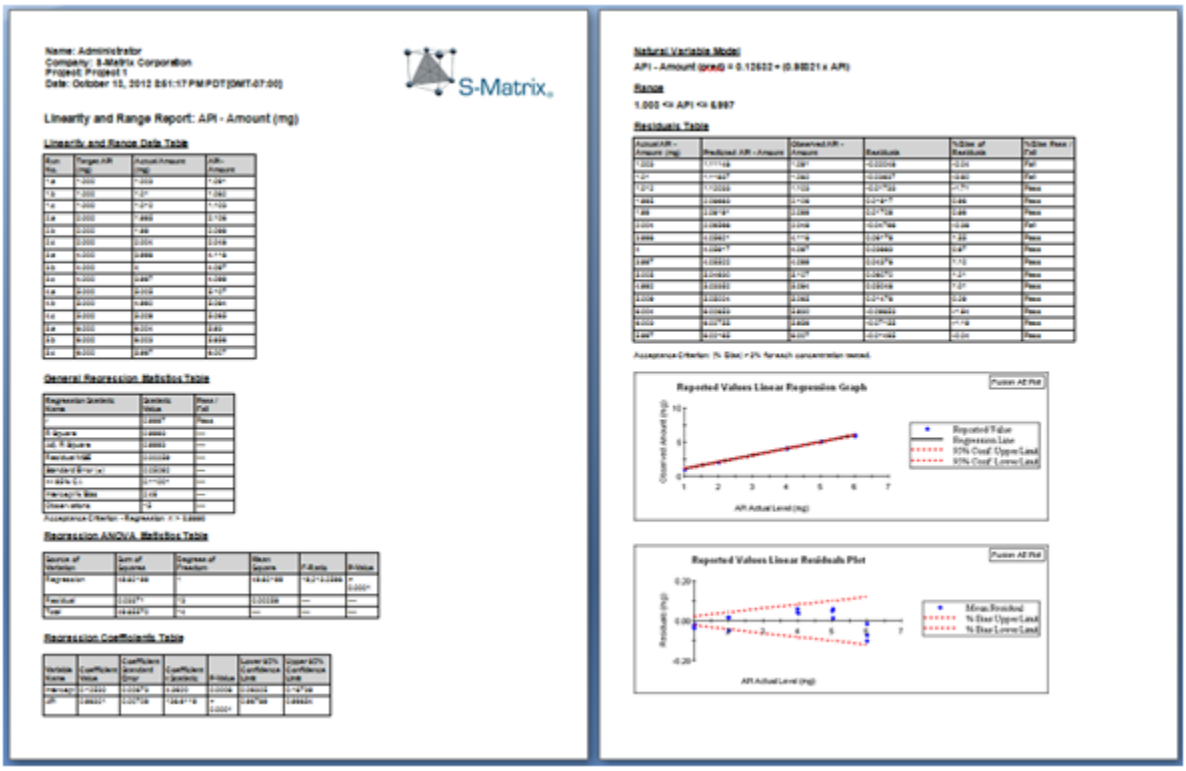
Step 5 – Fusion QbD Automatically Creates Final Reports and Graphs

ICH Q2(R1). LINEARITY

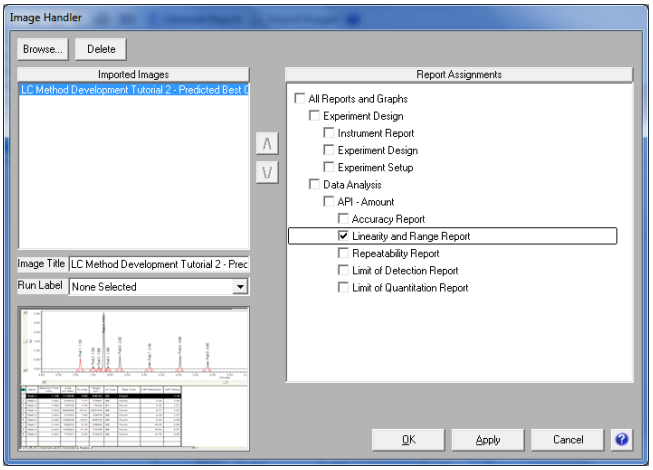
… If there is a linear relationship, test results should be evaluated by appropriate statistical methods, for example, by calculation of a regression line by the method of least squares…

The correlation coefficient, y-intercept, slope of the regression line, and residual sum of squares should be submitted. A plot of the data should be included…:

- Correlation Coefficient
- Y Intercept
- Slope of the Regression Line
- Residual Sum of Squares
- Linear Regression Plot
- Residuals Data Table and Plot



FMV enables you to include images of representative chromatograms into your final reports. You can associate these chromatogram images with any of the individual results reports which **FMV** automatically generates,



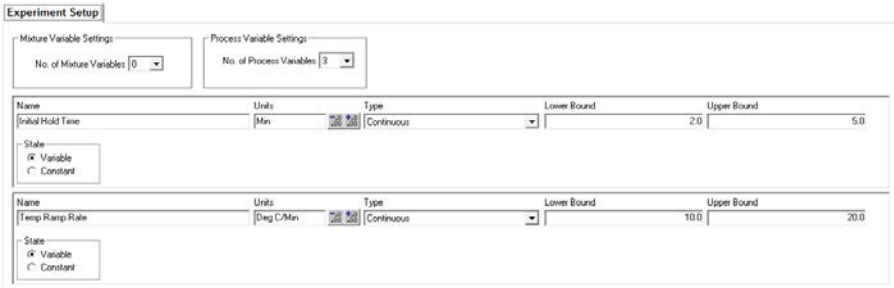
ICH Q2(R1):

For chromatographic procedures, representative chromatograms should be used to demonstrate specificity, and individual components should be appropriately labeled. If DL is determined based on visual evaluation or based on signal-to-noise ratio, the presentation of the relevant chromatograms is considered acceptable for justification.

Robustness Validation – DONE RIGHT!

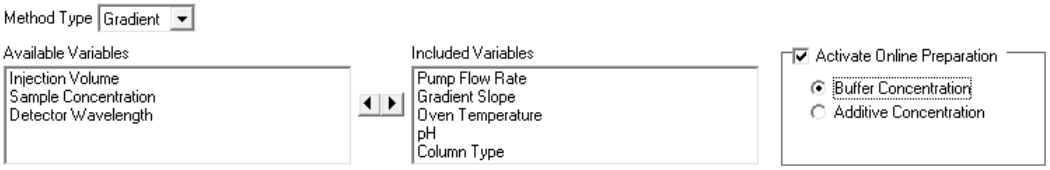
Experiment Setup – Non LC Robustness

You define the parameters to include in the **FMV** robustness experiment. **FMV** will automatically generate a statistically rigorous and defensible robustness design. **FMV** will instantly analyze all variable effects and test them for robustness according to your Pass/Fail criteria for each method performance characteristic you include in the analysis.



Experiment Setup – LC Robustness

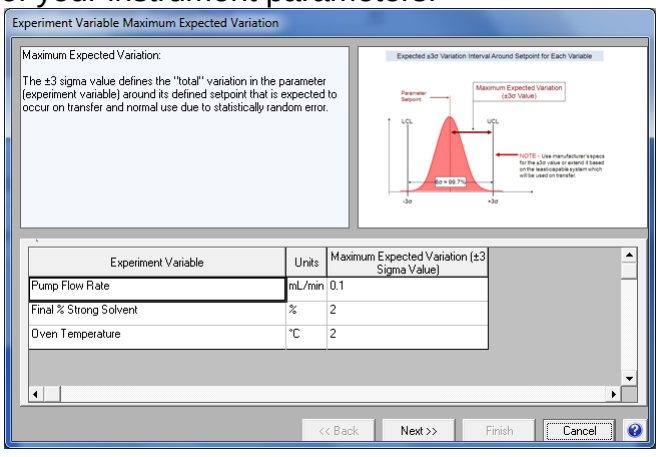
You select the parameters to include in the **FMV** robustness experiment. **FMV** will automatically generate the robustness design, re-construct it in the CDS as ready-to-run methods and sequence, import the chromatogram results directly from the CDS, re-map them to the robustness study, and instantly analyze, graph, and report the results.



The FMV Difference Lowers your Field Failure Risk

FMV robustness experiments let you use *valid experiment ranges for accurate, defensible estimates of parameter effects*.

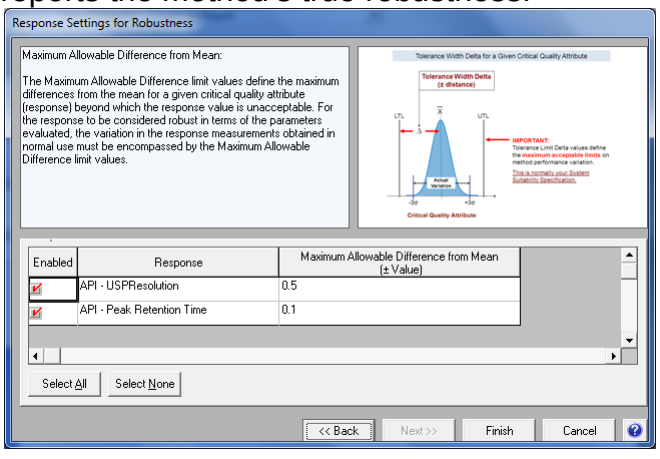
This avoids the risks associated with setting ranges equal to the expected variation ranges of your instrument parameters.



FMV robustness analysis wizard lets you set:

- expected parameter variation ranges
- acceptable performance limits for each key response

The wizard then accurately determines and reports the method's true robustness.



Robustness Validation – *Statistical Significance Testing* – Model Coefficients

Robustness Report: API - Area (*)

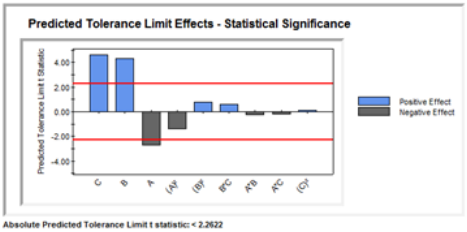
Coded Variable Name Key

Coded Variable Name	Actual Variable Name
A	Initial % Organic
B	Oven Temperature
C	pH

Variable Effects Table - Statistical Significance

Model Term	Robustness Testing Range (Coded)	Coefficient Value	Predicted Effect	Effect Standard Error	Effect t statistic	Pass/Fail
C	0.4000	161,391.4753	64,556.59	13,911.0838	4.6407	Fail
B	0.8000	74,520.8782	59,616.70	13,794.1618	4.3219	Fail
A	0.8000	-47,297.1750	-37,837.74	14,136.9455	-2.6765	Fail
(A)²	0.1600	-124,093.0600	-19,854.89	14,136.9455	-1.4045	Pass
(B)²	0.1600	64,847.5165	10,375.60	13,794.1618	0.7522	Pass
B*C	0.1600	50,247.7248	8,039.64	13,714.4961	0.5862	Pass
A*B	0.3200	-9,783.1120	-3,130.60	13,874.0259	-0.2256	Pass
A*C	0.1600	-13,383.4646	-2,141.35	14,022.6463	-0.1527	Pass
(C)²	0.0400	32,821.4015	1,312.86	13,911.0838	0.0944	Pass

Maximum Allowable Value: |Predicted Tolerance Limit t statistic| < 2.2622 for each variable studied.



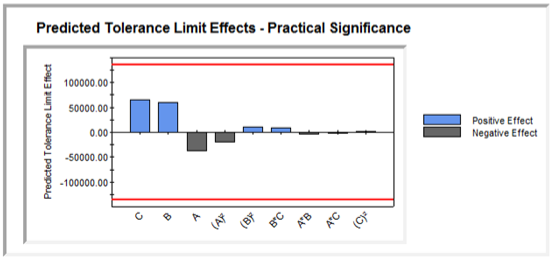
Absolute Predicted Tolerance Limit t statistic: < 2.2622

Robustness Validation – *Practical Significance Testing* – Effects Magnitude

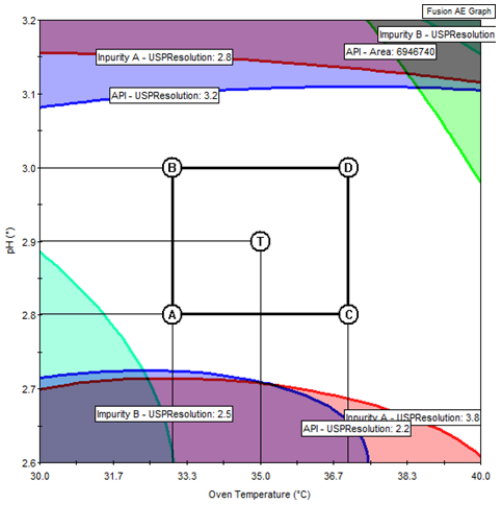
Variable Effects Table - Practical Significance

Model Term	Robustness Testing Range (Coded)	Coefficient Value	Predicted Effect	Pass/Fail
C	0.4000	161,391.4753	64,556.5901	Pass
B	0.8000	74,520.8782	59,616.7026	Pass
A	0.8000	-47,297.1750	-37,837.7400	Pass
(A)²	0.1600	-124,093.0600	-19,854.8896	Pass
(B)²	0.1600	64,847.5165	10,375.6026	Pass
B*C	0.1600	50,247.7248	8,039.6360	Pass
A*B	0.3200	-9,783.1120	-3,130.5958	Pass
A*C	0.1600	-13,383.4646	-2,141.3543	Pass
(C)²	0.0400	32,821.4015	1,312.8561	Pass

Maximum Allowable Difference from Mean: |Predicted Tolerance Limit Effect| < 136,200 for each variable studied.



Absolute Predicted Tolerance Limit Effect: < 136,200



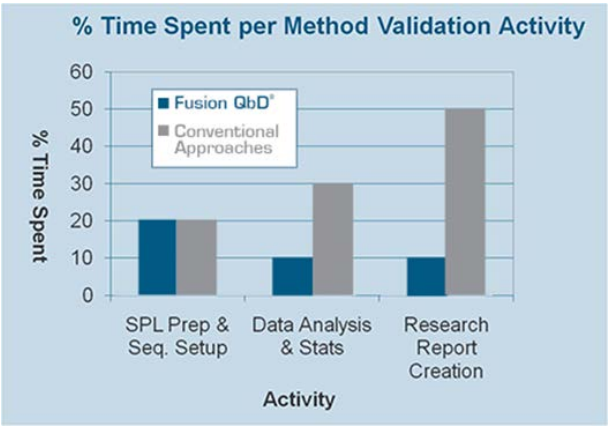
Automated LC Method Validation – Proven ROI

International Pharma Co. Benchmarking Project

Realized Time Savings = 85%.

Using historical records* and adjusting for project complexity

Minimum Expected Time Savings = 60%.



S-Matrix Software Products and Support

S-Matrix Corporation develops advanced Design of Experiment based-software that automates R&D experimental work according to Quality-by-Design principles and methodologies. S-Matrix's Fusion QbD platform automates and redefines experimentation in Analytical R&D, Chemical and Process R&D, Formulation, and Product R&D.

Fusion QbD Software System Product Suite

- **Fusion LC Method Development**
  Fully automated QbD experimenting on your LC system, integrated DOE, automated robustness simulation & chromatography data modeling. Chemistry screening without the need for peak tracking.
- **Fusion Analytical Method Validation**
  Meet regulatory guidelines with a best-practices approach toward LC method validation with comprehensive reporting. Also supports formal validation of Non-LC methods (e.g. GC, CE, Q-NMR).
- **Fusion Inhaler Testing**
  Create sampling plans, export and import data from your CDS via validated data exchange, calculate particle size distribution results, and generate reports according to USP 601, Ph.Eur. 2.9.18, and ISO 27427.
- **Fusion Product Development**
  The perfect QbD software for formulation & product development – automated experimental design selection, sophisticated analysis tools, including automated modeling and simulation, comprehensive reporting, with a full 21 CFR 11 compliance toolset.

Sales and Support

Sales: Tel: 800-336-8428 (Outside the USA: 707-441-0406). Email: Sales@smatrix.com
Customer Support: Tel: 707-441-0407. Fax: 707-441-0410. Email: Support@smatrix.com

On-site and Web Training

S-Matrix offers on-site training programs for installed systems. Training includes experiment strategies, experimental design (DOE), data analysis, graphical visualization and ranking of effects, numerical and graphical optimization, and QbD Reporting.

S-Matrix also offers interactive web training which covers software features and operation, along with general principles of DOE and QbD. Web training programs can be tailored to suit your individual focus and information requirements.

To arrange an on-site or web-based training program, call 707-441-0406.

S-Matrix Corporation
1594 Myrtle Avenue
Eureka, CA 95501 USA
www.smatrix.com