# **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
- 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

#### **Method Validation Experiment Suite**

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

Experiment Setup

Global Compound Settings

Assay Type

Compound Name

API

Sampling Plan

No. of Compounds 3

No. of Levels per Compound 5

Potency

Units

mg

Level Settings

80

90

100

110

120

Level 1

Level 2

Level 3

Level 4

Level 5

.00 .00

- 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 Simple 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**

- No. of Compounds
- No. of Levels per Compound
- 100% Standard Level
- Compound Name, Units, and Levels

#### 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
- Multi-level Bracketing Overlap

ultileve	ng - NonOve verage el Bracketing if Repeat Inje	Star - Ove	rfap s per Level 1	•	Standards Scheme No. of Standards per Group 1 • Hinjections Between Groups 3 •
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2	CAL -121		140		
3	CHK - 1.8		100	100	
	1.a	80	80	80	
5	1.6	80	80	80	
	1.c	80	80	80	
	CHK - 1.b		100	100	
	2.a	90	90	90	-
9	2.0	90	90	90	
	2.0 CHK+1.c	90	90	90	
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		_			
			ettings are valid.		

#### 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.

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Run No.	API (mg)	Impurity A	Impurity B (%)
CAL-L1.1			1.41
CAL - L2 1		-	
CHK-1A	100	100	100
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1.b	80	80	80
1.c	80	80	60
CRK-1.b	100	100	100
2.a	90	90	90
2.6	90	.90	90
2.c	90	90	90
CHK - 1.c	100	100	100
3.a	100	100	100
3.b	100	100	100
3.c	100	100	100
CHK-14	100	100	

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#### 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.

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3	1.c	1.000	1.012	0.2500		
-4	2.a	2.000	1.995	0.3500		
5	2.5	2,000	1.99	0.3500		
6	2.c	2.000	2.004	0.3500		
7	3.a	4.000	3.998	0.3600		
8	3.b	4.000	4.002	0.3600	-	
9	3.c	4.000	3.997	0.3600		
		5,000	5.005	0.4000		
	4b	5.000	4.992	0.4000		
	4.c	5.000	5.009	0.4000		
	5.a	6.000	6.004	0.4500	-	
	5.b	6.000	6.003	0.4500		
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#### Flexible Data Analysis Setup Wizard

- Associate different responses with different analyses – e.g.
  - Associate Amount results data with analysis of Accuracy
  - Associate Area results data with analysis of Linearity
- Include LOD and LOQ and select Calculation Method(s)
- Set Global and Level-specific Acceptance Criteria
- Including Level-specific Spec Limits for Raw Data

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#### 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

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**FMV** also enables you to include images of representative chromatograms into your final reports.

#### ICH Q2(R1):

For chromatographic procedures, representative chromatograms should be used to demonstrate specificity, and individual components should be appropriately labeled...

## **Robustness Validation – DONE RIGHT!**

#### Experiment Setup – LC Robustness Example

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.

Method Type Gradient		
Available Variables	Included Variables	Activate Online Preparation
Gradient Curve Gradient Slope Sample Concentration Additive Concentration Additive Type Column Type	Pump Flow Rate Injection Volume Owne Wavelength	C Buffer Concentration C Additive Concentration C D



Gradient Methods

- Normal Phase
- Ion Exchange
- Size Exclusion

FMD provides visual displays to simplify setup for complex settings such as required pump program conditions and key settings for each included column such as pH upper limit and conditioning time.

### 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.

E	xperiment Variable Maximum Expected Variation Maximum Expected Variation: The 33 sigma value defines the "total" variation in the p (experiment variable) around its defined setpoint that is occur on transfer and normal use due to statistically rank	to Parameter (230 Value)	
	Experiment Variable	Units	Maximum Expected Variation (±3 Sigma Value)
	Pump Flow Rate	mL/min	0.1
	Final % Strong Solvent	%	2
	Oven Temperature	°C	2
	•	<	< Back Next>> Finish Cancel @

**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.

Maximum A The Maximu differences (response) b	ettings for Robustness llowable Difference from Mear: um Allowable Difference limit values define from the mean for a given critical quality at beyond which the response value is unacc	tribute eptable. For	Televises With Data for a Over Ortical Duality Attribute Televises With Data State S
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#### Robustness Validation - Statistical Significance Testing - Model Coefficients

#### Robustness Report: API - Area (\*)

#### Coded Variable Name Key

Coded Variable Name	Actual Variable Name
A	Initial % Organic
В	Oven Temperature
с	pН

#### 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	Fai
В	0.8000	74,520.8782	59,616.70	13,794.1618	4.3219	Fai
A	0.8000	-47,297.1750	-37,837.74	14,136.9455	-2.6765	Fai
(A) <sup>2</sup>	0.1600	-124,093.0600	-19,854.89	14,136.9455	-1.4045	Pass
(B) <sup>2</sup>	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) <sup>2</sup>	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

### Robustness Validation - Practical Significance Testing - Effects Magnitude





### **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%.



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### **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: <u>Sales@smatrix.com</u> Customer Support: Tel: 707-441-0407. Fax: 707-441-0410. Email: <u>Support@smatrix.com</u>

### 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.

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