

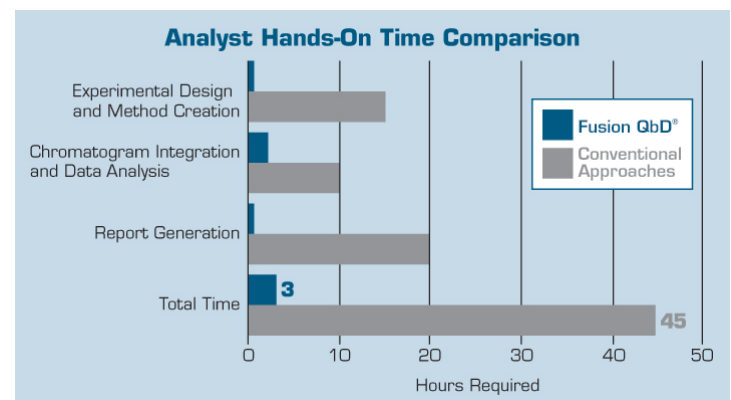
## Fusion Method Development

### Robust LC Method Development Software



### The Only Software That Has It All!

- **100% aligned with FDA/ICH Quality by Design (QbD) guidances!**
- **Fully automates QbD method development experiments on multiple instruments and CDS systems!**
- **Gives you knowledge – and statistical assurance – that you have the best performing and most robust method, not just incremental improvement!**
- **Can shorten LC method development time by as much as 75%!**



# Automated • QbD Aligned • LC Method Development

## Key Benefits of the Fusion QbD Software

### ➤ Quality by Design (QbD) Principles and Guidelines – **Built In!**

#### Formal Experimental Design – Built In

**ICH-Q8(R2)** – Formal Experimental Design – A structured, organized method for determining the relationship between factors affecting a process and the output of that process. Also known as “Design of Experiments”

#### Interaction Effects Characterization – Built In

**ICH Q8(R2)** – Information from formal experimental designs can be useful in identifying critical or interacting variables ...

#### Integrated Monte Carlo Simulation for Robustness – Built In

**FDA Reviewer Guidance – Validation of Chromatographic Methods** – ... methods should be validated and also designed by the developer or user to ensure ruggedness or robustness

**ICH Q2(R1)** – The evaluation of robustness should be considered during the development phase...

### ➤ Automated QbD-aligned Experimentation – **Built In!**

Experimental Design Wizard – examines your stage of work (screening or optimizing) and study parameters, then instantly generates the most efficient and defensible experiment design

#### Experiment Automation Wizards

- *Export Wizard* automatically builds your experimental design in the CDS as ready to run methods and sequence
- *Import Wizard* automatically imports all chromatogram results data from the CDS as analysis-ready data sets

Data Analysis & Modeling Wizard – automatically performs multiple integrated analyses, including experimental error, outlier, nonlinearity, and instantly builds statistically defensible models for all included method performance characteristics

### ➤ QbD Design and Operating Space Visualization — **Built In!**

Best Answer Search – instantly identify the best performing method overall in terms of simultaneously meeting all your studied method performance goals

Design Space – graphically visualize the QbD Design Space exactly as described in **ICH Q8(R2)**

Proven Acceptable Ranges – scribe onto your design space the operating ranges of your study parameters which meet all your method performance requirements

### ➤ 21 CFR Part 11 Compliance Support Toolset – **Built In!**

Automated and audited data exchanges with the CDS

E-record and E-signature controls with full work auditing

Workflow Management System with E-review and E-approve Capabilities

# Automated LC Method Development Experimentation – Five Step Workflow

1. You complete a simple experiment setup template.
2. Fusion QbD generates the experimental design and exports the design to the CDS.
3. The CDS runs the experiment on the target LC system.
4. Fusion QbD imports the chromatogram results from the CDS and analyzes the data.
5. Fusion QbD automatically creates final reports with QbD visualization graphics.

## Step 1 – You Complete the Template

**Fusion LC Method Development Software (FMD)** has simple experiment setup templates for method development experiments. **FMD** automatically adjusts the LC-centric template to the stage of the study – Screening or Optimization, the type of LC (e.g. Binary or Quaternary pump), and the type of chemistry (e.g. Reversed Phase, Ion Exchange, etc.).

### Select Your Study Parameters

Simply select the instrument and chemistry parameters to study. **FMD** adds settings controls for each parameter to the setup template so that you can define the range or levels you want to explore.

### Online Preparation (OLP)

OLP automates mobile phase preparation for Buffer Strength (shown at right), pH, or Salt Concentration. OLP configures the display for simple experiment setup, and (2) builds the proportioning required for each experiment run into the instrument methods it automatically constructs.

**Maintain target level in each run:** the software can maintain the target OLP variable in a given run (injection) as an absolute constant within the mobile phase independent of the change in the Strong/Weak solvent ratio across the gradient.

### Select Your Experiment Type

Pump Program

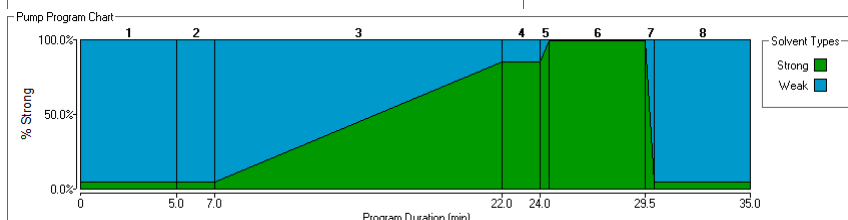
No. of Gradient Steps: 1

Time Precision: 0.00

No.	Step Name	Time State	Time - Lower Bound	Time - Upper Bound	% Strong Solvent
1	Equilibration	Constant	5.0	---	5.0
2	Initial Hold	Constant	2.0	---	5.0
3	Gradient	Constant	15.0	---	---
4	Final Hold	Constant	2.0	---	85.0
5	Ramp Up to Wash	Constant	0.5	---	---
6	Column Wash	Constant	5.0	---	99.0
7	Ramp Down from Wash	Constant	0.5	---	---
8	Re-equilibration	Constant	5.0	---	5.0

**FMD** supports Screening and Optimization studies for:

- Isocratic Methods
- Reversed Phase
- Chiral
- HILIC
- 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.

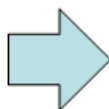
## Step 2 – Fusion QbD Generates the Experiment and Exports it to the CDS

**FMD** automatically constructs the experiment designs within the CDS as ready-to-run methods and sequences. It also automatically adds column conditioning for each included column to accommodate chemistry system changes between injection (e.g. strong solvent type and/or pH).

Name: Administrator  
Company: S-Matrix Corporation  
Project: Project 1  
Date: October 27, 2012 1:11:39 PM PDT [GMT 07:00]

**Experiment Design - Experiment 1**

Run No.	Sample Set No.	Gradient Time (min)	pH (F)	Column Type (F)
Condition Column - 1	1	2.0	2.0	C18
Condition Column - 2	1	2.0	2.0	Phenyl
Condition Column - 3	1	2.0	2.0	Amide
Condition Column - 4	1	2.0	2.0	CS
1	1	10.0	2.0	C18
2	1	2.0	2.0	C18
3	1	10.0	2.0	Phenyl
4	1	2.0	2.0	Phenyl
5	1	10.0	2.0	Amide
6	1	2.0	2.0	Amide
7	1	6.0	2.0	CS
8	1	6.0	2.0	CS
Condition Column - 5	1	2.0	3.6	C18
Condition Column - 6	1	2.0	3.6	Phenyl
Condition Column - 7	1	2.0	3.6	Amide
Condition Column - 8	1	2.0	3.6	CS

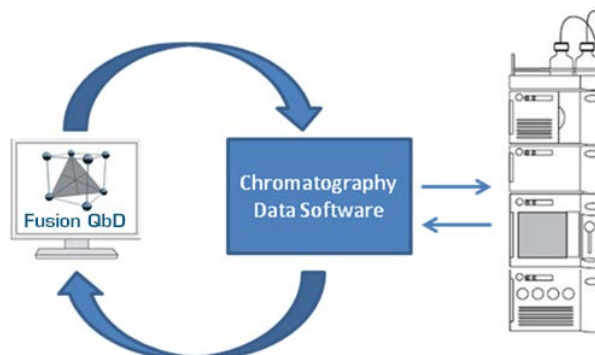


Example Sample Set in S-Matrix/FMD Screening Expt as System Administrator - Sample Set Method Editor

Plate/Vial	PL (F)	# of Rls	Label	Sample Name	Function	Method Set / Report Method	Run Time (minutes)	Data Start (minutes)	Next Rl Delay (minutes)	Column Position	Dilution
1					Condition Column	Example Sample Set 001_097	0.00	0.00	0.00	Position 1	
2					Condition Column	Example Sample Set 001_098	0.00	0.00	0.00	Position 2	
3					Condition Column	Example Sample Set 001_099	0.00	0.00	0.00	Position 3	
4					Condition Column	Example Sample Set 001_100	0.00	0.00	0.00	Position 4	
5					Condition Column	Example Sample Set 001_101	0.10	0.00	0.00	Position 1	
6					Equilibrate	Example Sample Set 001_101	10.00	0.00	0.00	No Change	
7	F.A.1	1.0	1	Unk-000-000 Blank - 1	Inject Samples	Example Sample Set 001_101	11.00	0.00	1.50		1.00000
8					Condition Column	Example Sample Set 001_102	0.10	0.00	0.00	Position 2	
9					Equilibrate	Example Sample Set 001_102	3.00	0.00	0.00	No Change	
10	F.A.1	1.0	1	Unk-000-000 Blank - 2	Inject Samples	Example Sample Set 001_102	11.00	0.00	1.50		1.00000
11					Condition Column	Example Sample Set 001_103	0.10	0.00	0.00	Position 3	
12					Equilibrate	Example Sample Set 001_103	3.00	0.00	0.00	No Change	
13	F.A.1	1.0	1	Unk-000-000 Blank - 3	Inject Samples	Example Sample Set 001_103	11.00	0.00	1.50		1.00000
14					Condition Column	Example Sample Set 001_104	0.10	0.00	0.00	Position 4	
15					Equilibrate	Example Sample Set 001_104	3.00	0.00	0.00	No Change	
16	F.A.1	1.0	1	Unk-000-000 Blank - 4	Inject Samples	Example Sample Set 001_104	11.00	0.00	1.50		1.00000
17					Condition Column	Example Sample Set 001_001	0.10	0.00	0.00	Position 1	
18					Equilibrate	Example Sample Set 001_001	3.00	0.00	0.00	No Change	
19	F.A.2	1.0	1	Unk-001-001 1	Inject Samples	Example Sample Set 001_001	11.00	0.00	1.50		1.00000
20					Condition Column	Example Sample Set 001_002	0.10	0.00	0.00	No Change	
21	F.A.2	1.0	1	Unk-001-002 2	Inject Samples	Example Sample Set 001_002	3.00	0.00	0.00	No Change	
22					Equilibrate	Example Sample Set 001_002	0.00	0.00	0.00	No Change	
23					Condition Column	Example Sample Set 001_003	0.10	0.00	0.00	Position 2	
24					Equilibrate	Example Sample Set 001_003	3.00	0.00	0.00	No Change	

## 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

**FMD** automatically imports the required peak result data from the CDS, and re-maps the results to the design for automated analysis, graphing, and reporting.

S-Matrix/FMD Screening Expt/FMD Screening - Results/FMD Screening Design

Channel: PDA Ch1 254nm@1.2nm

Trend Responses

	Operator	Value	Response
1	<input checked="" type="checkbox"/> No. of Peaks >=		
2	<input checked="" type="checkbox"/> No. of Peaks >=	1.50	USPResolution
3	<input checked="" type="checkbox"/> No. of Peaks >=	2.00	USPResolution
4	<input checked="" type="checkbox"/> No. of Peaks <=	1.20	USPTailing
5	<input checked="" type="checkbox"/> Max Peak #	1	USPResolution

Select All Select None I = Incomplete D = Duplicate

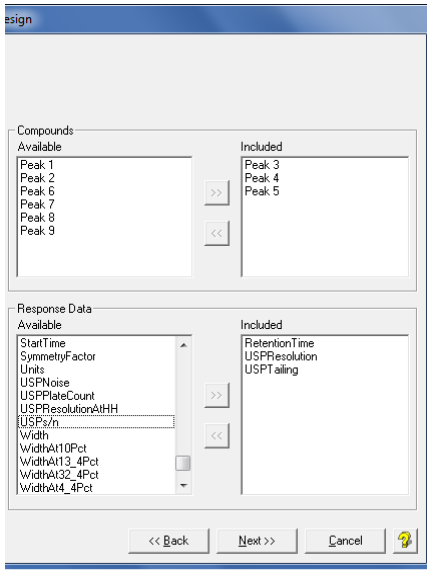
## Patented Trend Responses™ – Screening Experiments

**FMD's** unique and patented Trend Responses eliminate the requirement for laborious and error-prone peak tracking in initial screening experiments. Flexible Trend Response operators enable you to automatically retrieve data for any separation characteristics you want to evaluate. Example Trend Responses which **FMD** can instantly obtain from the experiment chromatograms include:

- No. of Integrated Peaks
- No. of Baseline Resolved Peaks
- No. of Peaks with Acceptable Tailing

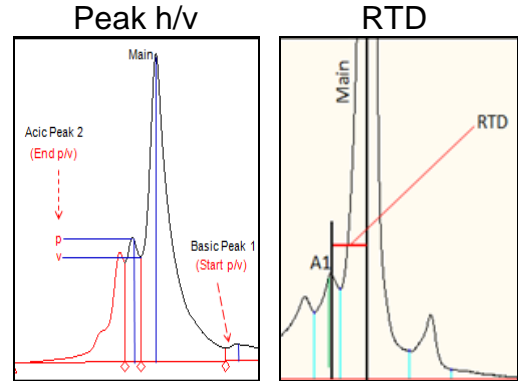
**FMD's** "Max Peak" operator can automatically track your APIs, or Main Peaks, and import all responses of interest for this peak, including Retention Time, Resolution, etc.

## Named Peak Responses – Optimization Experiments



**FMD** can import and model any results data computed by the CDS for named peaks. You select the results which correspond to your critical method performance characteristics. These are your Critical Quality Attributes (CQA) in QbD terminology!

**FMD** also supports large molecule separation metrics for poorly resolved peaks such as Peak Height-to-Valley Ratios (Peak h/v) and Retention Time Difference (RTD).



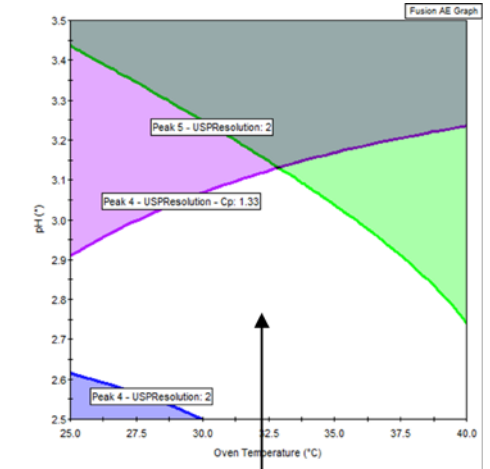
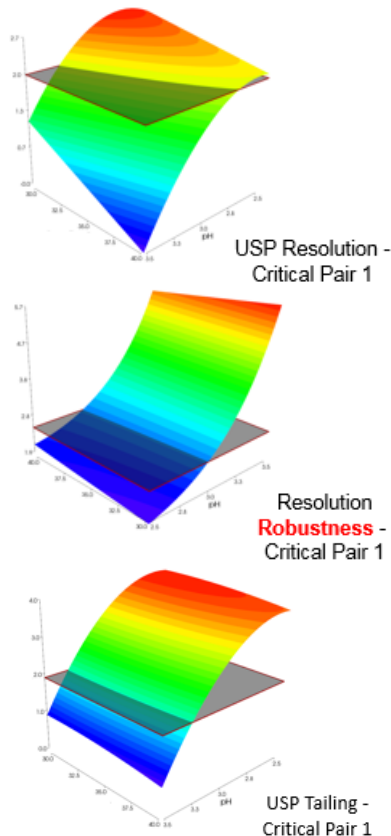
## Best Answer Searches

You set the required performance goals for all your modeled CQAs. **FMD's** search engine then comprehensively examines the performance of all possible methods that exist within the combined ranges of your experiment variables to identify the method which meets or exceeds your goals.

## Patented Robustness Simulator™

All modeling software can only directly predict the mean, or average, performance of a given method. That is why **FMD's** Robustness Simulator is so critical to developing your final robust design space.

Robustness Simulator uses a correctly-implemented Monte Carlo simulation engine to automatically compute method robustness metrics for all CQAs in your optimization experiment. It graphically shows variable combinations which do not meet mean performance or robustness requirements (shaded regions) – and your final robust design space (un-shaded region) – where methods simultaneously meet requirements for mean chromatographic performance and robustness!



## Design Space –

joint region of acceptable method mean performance and robustness.

## Step 5 – Fusion QbD Automatically Creates Final Reports with QbD Visualization Graphics

**FMD** enables you to graphically present your final design space in terms of all your critical method performance attributes (CQAs). A color is assigned to each CQA, and the region of the graph shaded with the color corresponds to methods which do not meet the goal for that CQA.



Here you can select which experiment variables to graph. Slider controls for numeric variables and List Controls for non-numeric variables (e.g. Column Type) allow you to see how the design space shape changes as you change variable settings.

The screenshot displays the Fusion QbD software interface. On the left, there are several configuration panels: 'Reports' (set to 'DS - OS - 15% Organic'), 'Graph Settings' (listing variables like Initial % Organic and Oven Temperature), 'Verification Run Settings' (with a checked 'Include Bounded Operating Space'), and 'Verification Runs' (a table of runs A, B, C, D, T). The main 'Graph' area shows a 2D plot of Oven Temperature (°C) vs. Initial % Organic (%). The design space is a shaded region bounded by points A, B, C, D, and T. A 'Fusion AE Graph' is overlaid, showing a peak at 13.3 minutes. Below the graph is a 'Response Settings' table:

Name	Goal	Lower Bound	Upper Bound	Target Predictions	Pointer Predictions	Contour Label	Color
Peak 3 - USPResolution	Maximize	2.00		3.54			Red
Peak 4 - USPResolution	Maximize	1.50		2.60			Blue
Peak 5 - USPResolution	Maximize	2.00		2.21			Green
Peak 6 - USPResolution	Target	0.90	1.10	1.00			Orange
Peak 3 - USPResolution - Cp	Maximize	1.33		1.66			Teal
Peak 4 - USPResolution - Cp	Maximize	1.33		1.78			Purple
Peak 5 - USPResolution - Cp	Maximize	1.33		2.51			Light
Peak 6 - USPResolution - Cp	Maximize	1.33		4.15			Dark



Easily add a graphical display of your Proven Acceptable Ranges (PARs) within your design space.



Here you can dynamically input and update your CQA goals.

The screenshot shows a final report titled 'Final Design Space & PARs' from S-Matrix. It includes a header with project information (Company: S-Matrix, Project: Project 1, Date: May 26, 2015 4:06:54 PM PDT [GMT-07:00]). The main content features three small graphs showing the design space for different levels of a non-graphed variable (pH). Below these are sections for 'Operating Space Settings', 'Response Variable Goals', 'Study Variable Settings', and 'Experiment Constants'. The 'Response Variable Goals' table is as follows:

Name	Unit	Goal	Lower Bound	Upper Bound	Color
API - USPResolution		Maximize	2.00		Purple
Impurity A - USPResolution		Maximize	2.00		Blue
Impurity B - USPResolution		Maximize	2.00		Green
API - USPResolution - Cp		Target	0.90	1.10	Orange
Impurity A - USPResolution - Cp		Maximize	1.33		Teal
Impurity B - USPResolution - Cp		Maximize	1.33		Purple
API - USPResolution - Cp		Maximize	1.33		Light
Impurity B - USPResolution - Cp		Maximize	1.33		Dark

Create any number of Graphical Answer Search reports, with each report containing a unique overlay graph representing the Design Space and Proven Acceptable Ranges at different level setting combinations of critical method parameters. For example, given three study variables you could create three reports with a graph in each to display the continuity of the PAR across the operating range of a non-graphed variable – as shown below for pH.

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

The screenshot shows the 'Image Handler' software interface. It has a 'Browse' button and a 'Delete' button. Below these are 'Imported Images' and 'Report Assignments' sections. The 'Report Assignments' section has several checkboxes: 'All Reports and Graphs', 'Equipment Design', 'Instrument Report', 'Experiment Design', 'Equipment Setup', 'Data Analysis', 'API - Amount', 'Accuracy Report', 'Linearity and Range Report', 'Repeatability Report', 'Limit of Detection Report', and 'Limit of Quantitation Report'. The 'Linearity and Range Report' checkbox is checked. At the bottom, there are 'OK', 'Apply', and 'Cancel' buttons.

# Automated QbD Experiments – Supported Platforms

## Agilent ChemStation/OpenLAB and Waters Empower

### Pumps

G1310A-C  
G1311A-C  
G1312A-C  
G4220A-B  
G4204A  
G4302A  
G5611A

### Automatic Liquid Sampler (ALS)

G1313A  
G1321A-C  
G1329A-B  
G1367A-E  
G4226A  
G4303A  
G5667A

### Detectors

G1314A-D  
G1315A-D  
G1365A-D  
G4212A-B

### Valves

G1157A  
G1158A  
G1159A  
G1160A  
G1170A (as Column Valve Drive with 2, 4, or 6  
position Valve Head)  
G1170A (as Solvent Valve Drive with 8 or 12  
position Valve Head)

### Thermostatted Column Compartment (TCC)

G1316A-C (2, 4, or 6 position column  
switching)

### Column Compartment Cluster (CCC)

G1316C x 2 (8 position column switching)

### Pump Valve Cluster (PVC)

G1160A or G1170A with 12 position Valve  
Head

**NEW** G7xxx – Agilent Infinity II Modules

\* – requires separate Fusion QbD Support Pack

## Waters Empower

### HPLC Modules

Waters 2690/2695 Alliance  
Waters 2996 PDA Detector  
Waters 2790/2795 Alliance  
Waters 2998 PDA Detector  
Waters 600 Pump Controller  
Waters 715/717 WISP Injector  
External Switching Valves (contact closure)  
Waters busLAC/E + SAT/IN (2)

### ACQUITY UPLC Modules

Acquity Binary Solvent Manager  
Acquity Sample Manager  
Acquity Column Manager  
Acquity Column Heater  
Acquity Column Heater/Cooler  
External Switching Valves (contact closure)  
Acquity TUV Detector  
Acquity PDA Detector  
Waters 2998 PDA Detector  
Waters 2996 Detector  
Waters 996 PDA Detector (uncontrolled)  
Acquity FLR Detector (uncontrolled)  
Acquity ELS Detector (uncontrolled)  
H-Class FTN Sample Manager (Standard & Bio)  
H-Class Quaternary Solvent Manager (Standard & Bio)  
H-Class Column Manager (Standard & Bio)  
Acquity Sample Organizer

**NEW** Acquity UPC<sup>2</sup> SFC System\*

\* – requires separate Fusion QbD Support Pack

# S-Matrix Software Products and Support

S-Matrix Corporation develops advanced 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](mailto:Sales@smatrix.com)  
Customer Support: Tel: 707-441-0407. Fax: 707-441-0410. Email: [Support@smatrix.com](mailto: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.

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