

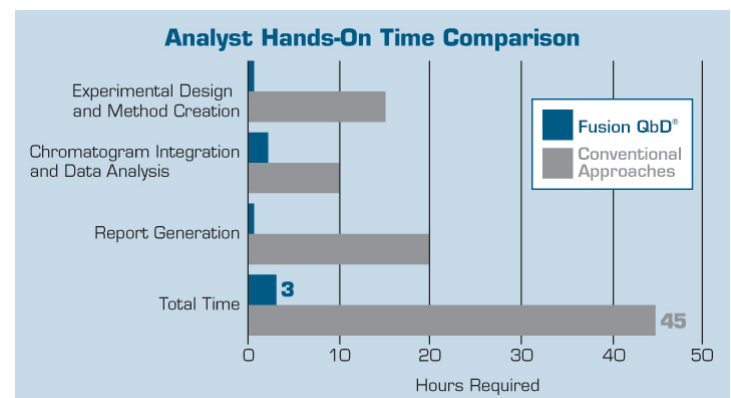
Fusion Method Development

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 at least 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 statistical 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 Robust Design Space (also called Method Operable Design Region – MODR) exactly as described in **ICH Q8(R2)**

Proven Acceptable Ranges – add the study parameter operating ranges which meet all your method performance requirements directly onto your design space graph

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

Automated and fully audited bi-directional 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 Experiment Type

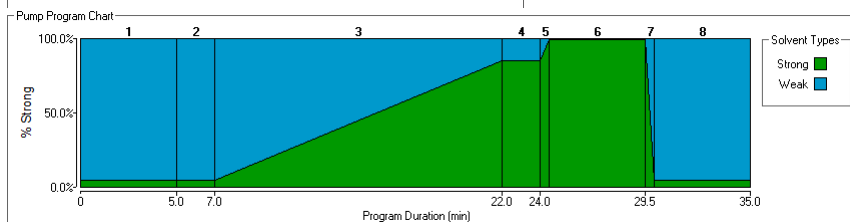
Pump Program

No. of Gradient Steps: 1 Time Precision: 0.01

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

Select Your Study Parameters

Experiment Setup | Sampling Plan

Method Type: Gradient

Available Variables: Gradient Curve, Gradient Slope, Sample Concentration, Additive Concentration, Additive Type, Column Type

Included Variables: Pump Flow Rate, Injection Volume, Oven Temperature, Wavelength

Activate Online Preparation
 Buffer Concentration
 Additive Concentration
 pH

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 pH (shown at right), Buffer Strength, Additive Concentration, 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.

Buffer Selector

pH Online Blending Mode: One Acid/One Base Pair pKa of Primary Compound

pH Buffer Settings

No. of Levels: 6

Buffer	Buffer Name	pH Level	Acid %	Base %
Acid	Formic Acid (20 mM)	2.73	100.0	0.0
Base	Ammonium Formate (20 mM)	3.00	85.0	15.0
		3.53	55.0	45.0
		3.99	30.0	70.0
		4.42	15.0	85.0
		4.93	5.0	95.0

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.

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

FMD automatically constructs the experiment designs within the CDS as ready-to-run methods and sequences. It also automatically orders the design for fast, efficient execution and adds column conditioning for chemistry system changes between injections (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 (p)	Column Type
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	8.0	2.0	CS
8	1	8.0	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

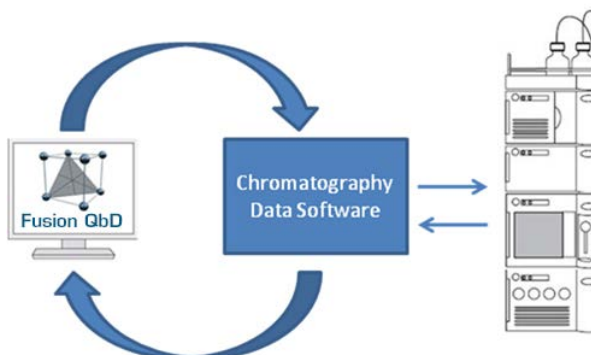
Plate/Vial	PL (mL)	Vol (mL)	Label	Sample Name	Function	Method Set / Report Method	Run Time (Minutes)	Data Start (Minutes)	Next Inj. Delay (Minutes)	Column Position	Dilution
1					Condition Column	Example Sample Set 001_097	8.00	0.00	0.00	Position 1	
2					Condition Column	Example Sample Set 001_098	8.00	0.00	0.00	Position 2	
3					Condition Column	Example Sample Set 001_099	8.00	0.00	0.00	Position 3	
4					Condition Column	Example Sample Set 001_100	8.00	0.00	0.00	Position 4	
5					Condition Column	Example Sample Set 001_101	9.10	0.00	0.00	Position 1	
6					Equilibrate	Example Sample Set 001_101	10.00	0.00	0.00	No Change	
7	I.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	I.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	I.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	I.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	I.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					Equilibrate	Example Sample Set 001_002	3.00	0.00	0.00	No Change	
22	I.A.2	1.0	1	Unk-001-002	2	Inject Samples	Example Sample Set 001_002	8.00	0.00	1.50	1.00000
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	USPRResolution
3	<input checked="" type="checkbox"/> No. of Peaks >=	2.00	USPRResolution
4	<input checked="" type="checkbox"/> No. of Peaks <=	1.20	USPTailing
5	<input checked="" type="checkbox"/> Max Peak #	1	USPRResolution

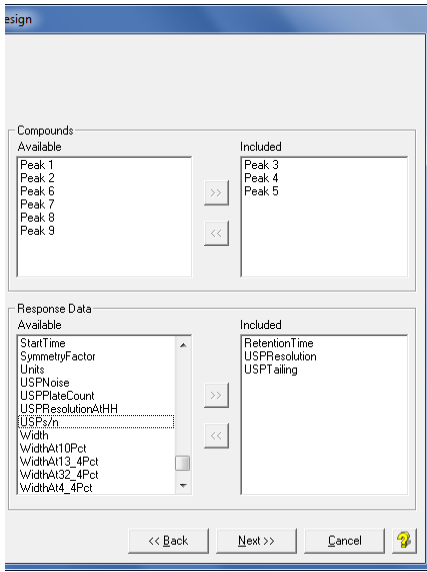
Select All Select None I = Incomplete D = Duplicate

Patented Trend Responses™ – Screening Experiments

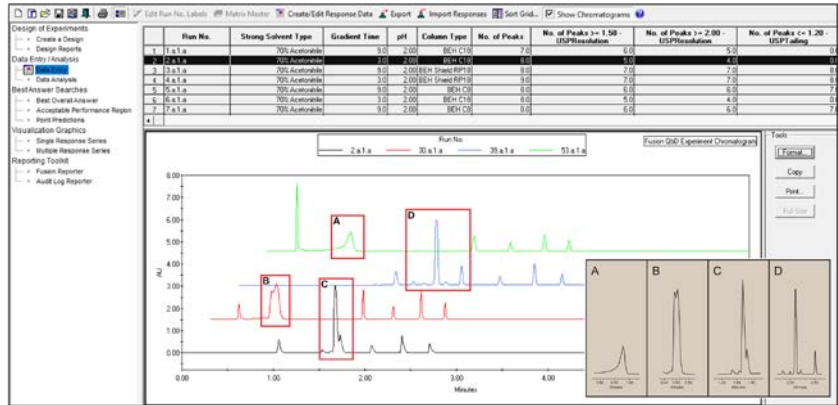
FMD's patented Trend Responses eliminate the requirement for laborious and error-prone peak tracking in initial screening experiments. Flexible Trend Response operators enable you to automatically retrieve data for any separation characteristics you want to evaluate. **Example Trend Responses** which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

Overall Selectivity Metrics	Auto Peak Tracking Results
No. of Integrated Peaks	Main Peaks – all specified results
No. of Baseline Resolved Peaks	Post Peaks – (elute after main peaks) all specified results
No. of Peaks with Good Tailing	First Peak – all specified results
No. of Peaks with Specified S/N Ratio	Last Peak – all specified results

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!



Best Answer Search

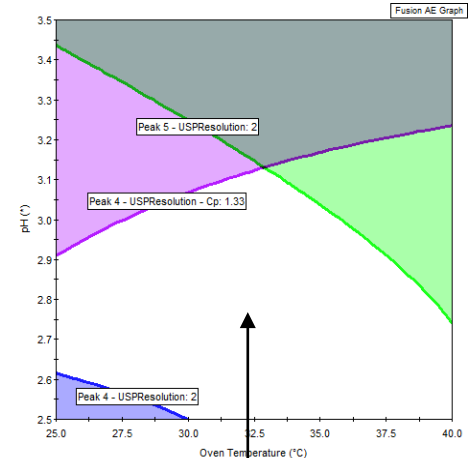
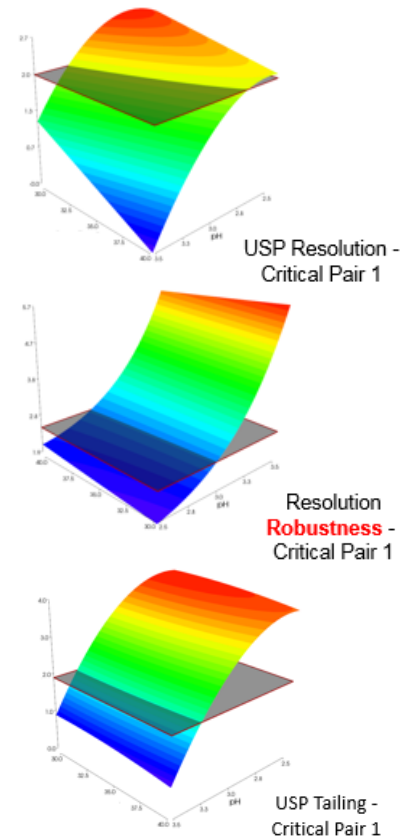
You set the required performance goals for all your modeled CQAs. **FMD's** search engine then comprehensively examines the performance of all possible methods that exist within the combined ranges of your experiment variables to identify the method which meets or exceeds your goals.

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:

- (1) automatically compute accepted method robustness metrics (e.g. C_p , C_{pk} , C_{pm} , C_{pkm}) for all CQAs in your optimization experiment.
- (2) Graphically show all methods which simultaneously meet all your requirements for mean performance and robustness – the unshaded regions in your final robust design space!



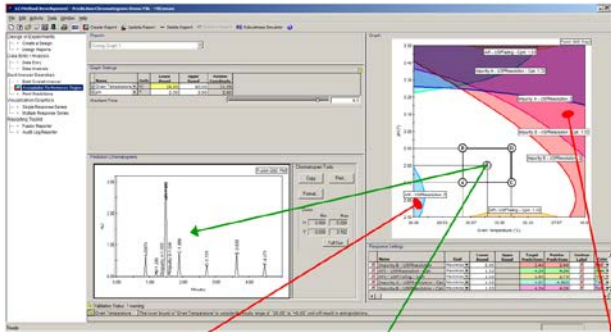
Design Space – Method Operable Design Region (MODR) – joint region of acceptable mean performance and method robustness.

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

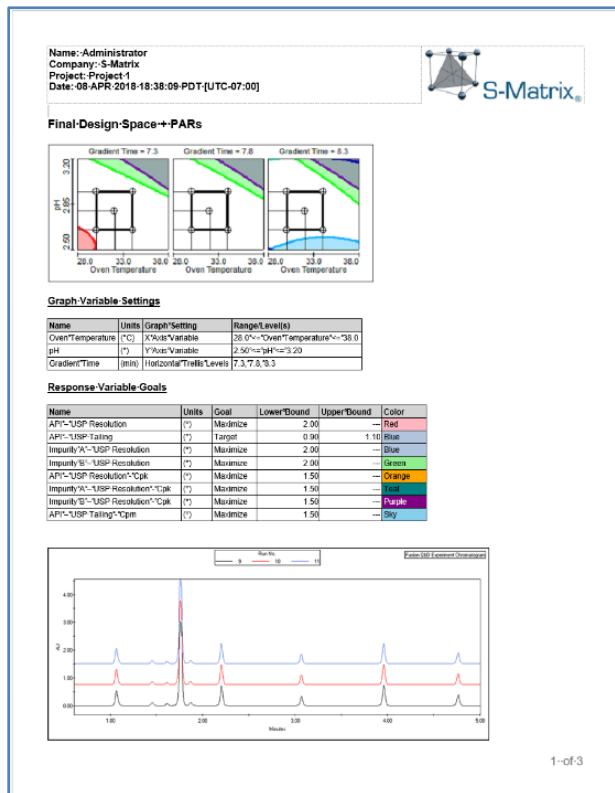
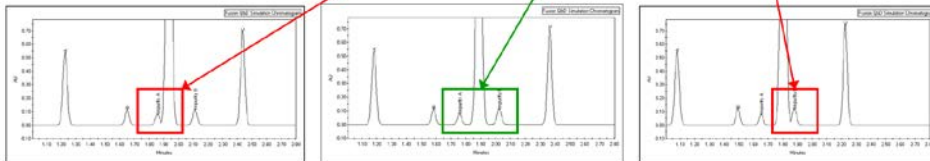
FMD enables you to graphically present your final design space in terms of all your critical method performance attributes (CQAs). A color is assigned to each CQA, and the region of the graph shaded with the color corresponds to methods which do not meet the goal for that CQA.



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.

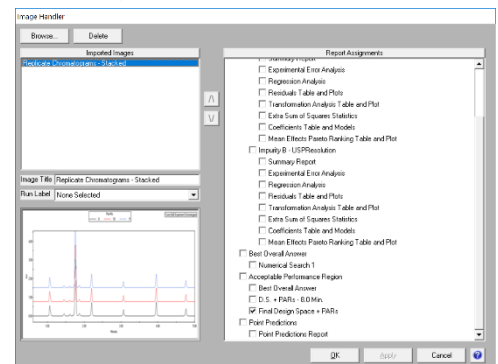


Just move your cursor around the Fusion QbD robust design space graph and see the simulation chromatogram update in real time to visualize the changes in method performance across the graph.



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.



Automated QbD Experiments – Supported Platforms

Supported Agilent LC Systems

- ✓ Solvent Selection Valves
- ✓ Column Switching Valves

Agilent 1100s
And 1200s



Agilent 1260
Infinity Series



Agilent 1260
Infinity II Series



Agilent 1290
Infinity Series



Agilent 1290
Infinity II Series



Supported Thermo LC Systems

- ✓ Solvent Selection Valves
- ✓ Column Switching Valves

UltiMate LCs



Vanquish Horizon
And Flex LCs



Supported Waters LC Systems

- ✓ Solvent Selection Valves
- ✓ Column Switching Valves

Alliance HPLC



Acquity Binary



Acquity H-Class



Acquity Arc



Acquity UPC²



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

Automated QbD experimenting on your LC – automated experimental design, integrated data modeling & robustness simulation. Supports all phases of method development from initial sample/method workup and chemistry scouting through robust method optimization.

■ 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

Build simple workflow templates, automate testing and data capture with your CDS via validated and fully audited data exchanges, correctly calculate all 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-aligned software for formulation & process development and Non-LC methods development – wizard driven experimental design, automated analysis and modeling, integrated Monte Carlo robustness simulation, elegant effects visualization graphics, and comprehensive reporting.

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.

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