

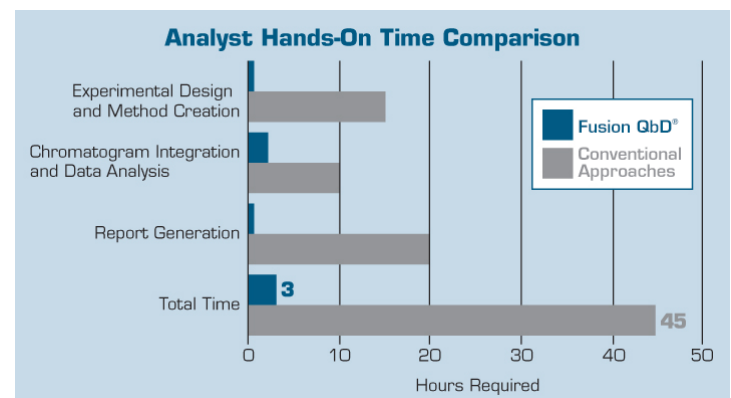
Fusion Method Development

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

Experiment Setup | Sampling Plan

Method Type: Gradient

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

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

Activate Online Preparation

Salt Concentration
 Buffer Concentration
 Additive Concentration

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.

Activate Online Preparation (OLP)

Activating OLP will (1) add the Stock Solution control to the setup display, and (2) reconfigure the Solvent Settings control panel to accommodate the required Stock Solution mobile phases.

Online Preparation Stock Solution

Stock Solution Name	Units	Amt/Conc.	Associated Solvent Type
Stock Solution	mM	100.0	Weak

Name: Buffer Concentration | Units: mM | Type: Discrete Numeric | Target Level: 1.0, 5.0, 10.0

State: Variable Constant

No. of Levels: 3

Maintain target level in each run.

Include "Type" Variable

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

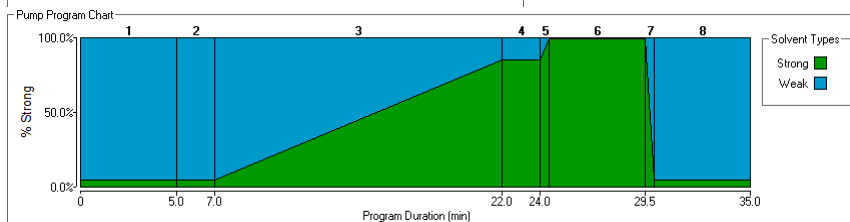
No. of Gradient Steps: 1

Time Precision: 0.01

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.

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 (I)	Column Type (I)
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

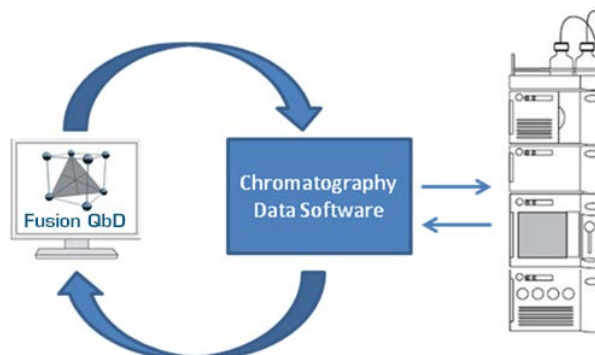


Example Sample Set in S-Matrix/FMD Screening Expt as System Administrator - Sample Set Method Editor

Run No.	Plate/Vial	PL (I)	# 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	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	0.00	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	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

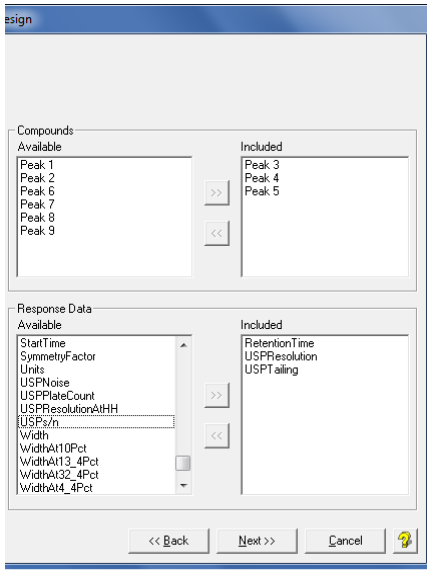
Patented Trend Responses™ – Screening Experiments

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

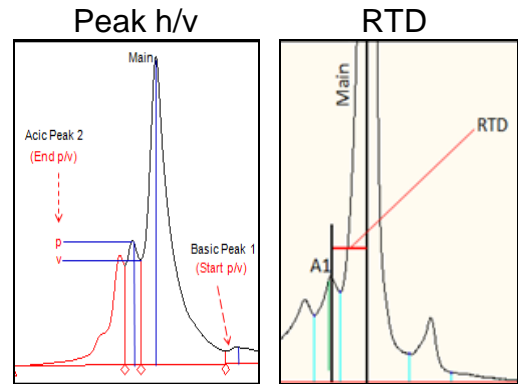
FMD's "Max Peak" operator can automatically track your API, or Main Peak, and import all responses of interest for this peak, including Retention Time, Resolution, etc.

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).



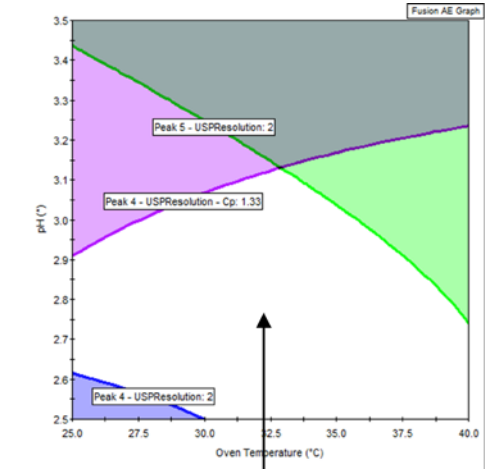
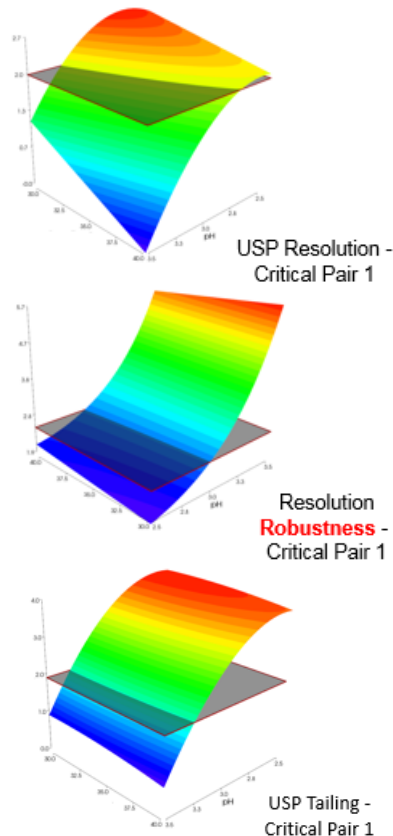
Best Answer Searches

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.

Reports

DS - OS - 15% Organic

Graph Settings

Name	Units	Lower Bound	Upper Bound	Pointer Coordinate
X Initial % Organic	%	8.0	15.0	
Y Oven Temperature	°C	30.0	38.0	

pH

Verification Run Settings

Include Bounded Operating Space

Operating Ranges

Variable	Lower Bound	Upper Bound	Center Point
Initial % Organic	8.0	12.0	10.0
Oven Temperature	32.0	37.0	35.0

Verification Runs Show Verification Run Labels

Point	Run ID	Initial % Organic	Oven Temperature	pH
A	DS - OS - 15% O	8.0	33.0	2.900
B	DS - OS - 15% O	8.0	37.0	2.900
C	DS - OS - 15% O	12.0	33.0	2.900
D	DS - OS - 15% O	12.0	37.0	2.900
T	DS - OS - 15% O	10.0	35.0	2.900

Graph

Response Settings

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			Lime
Peak 6 - USPResolution - Cp	Maximize	1.33		4.15			Blue



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.

Name: Administrator
Company: S-Matrix
Project: Project 1
Date: June 27, 2015 8:58:01 PM PDT [GMT-07:00]

S-Matrix

Overlay Graphics - Tralls - Initial % Organic

Operating Range Settings

Axis Name	Lower Bound	Upper Bound	Center Point
X Oven Temperature	25.0	37.0	32.0
Y pH	2.5	3.5	3.0

Response Variable Goals

Name	Units	Goal	Lower Bound	Upper Bound	Predicted Constraints
Peak 3 - USPResolution	%	Maximize	2.00		0.00
Peak 4 - USPResolution	%	Maximize	2.00		0.00
Peak 5 - USPResolution	%	Maximize	2.00		0.00
Peak 6 - USPResolution	%	Target	0.90	1.10	0.00
Peak 3 - USPResolution - Cp	%	Maximize	1.33		0.00
Peak 4 - USPResolution - Cp	%	Maximize	1.33		0.00
Peak 5 - USPResolution - Cp	%	Maximize	1.33		0.00
Peak 6 - USPResolution - Cp	%	Maximize	1.33		0.00

Study Variable Settings

Name	Units	Graph Setting	Range/Limits
Oven Temperature	°C	Factor Variable	25.0 to 40.0
pH		Factor Variable	2.5 to 3.5
Initial % Organic	%	Constant	11.0 to 15.0

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.

Image Manager

Source: Delete

Importer/Viewer

Image List [C:\Method Development\Fusion 2 - Proj] Run Label: None Selected

Report Assignments

- All Reports and Graphs
- Experiment Design
- Instrument Profile
- Equipment Design
- Equipment Setup
- Data Analysis
- API - Assay
- Assay Report
- Usability and Range Report
- Responsibility Report
- Link of Deviation Report
- Link of Quantitation Report

OK Apply Cancel

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
G1329A-B
G1367A-E
G4226A
G4303A
G5667A

Diode Array Detectors

G1315A-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

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

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
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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