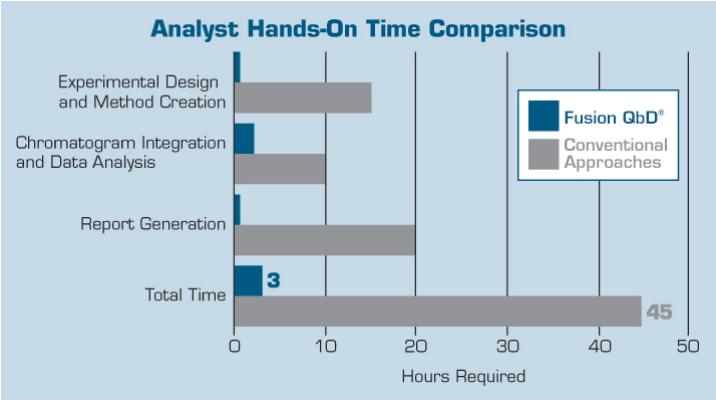
Fusion QbD® Software System

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%!**



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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

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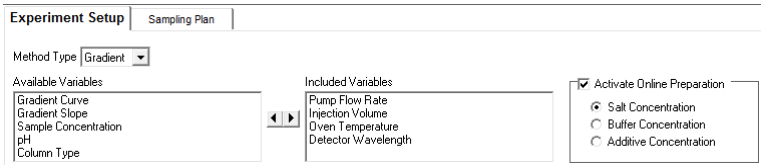
Automated LC Method Development Experimentation – Five Step Workflow

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.).

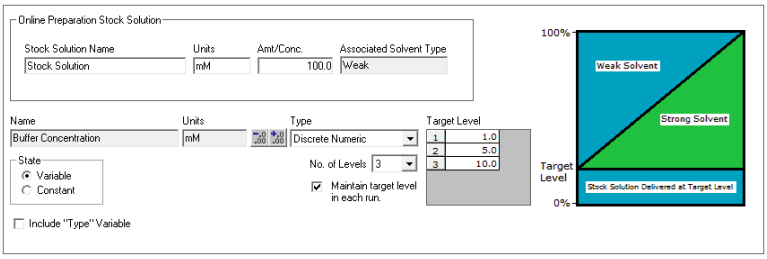
Select Your Study Parameters



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.

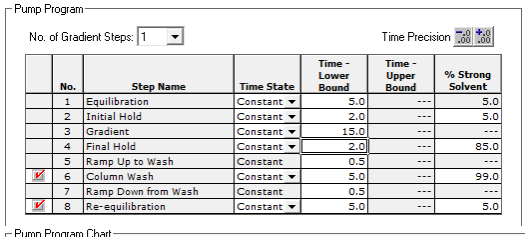
Activate Online Preparation (OLP)

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.



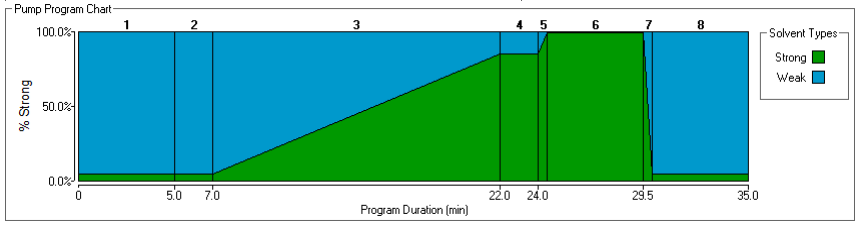
Maintain target level in each run: the software can maintain the target OLP variable in a given run (injection) as an absolute constant within the mobile phase independent of the change in the Strong/Weak solvent ratio across the gradient.

Select Your Experiment Type



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.

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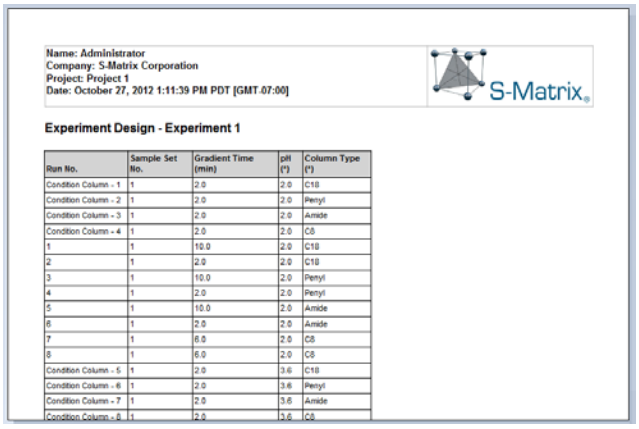
Step 2 – Fusion QbD Generates the Experiment and Exports it to the CDS

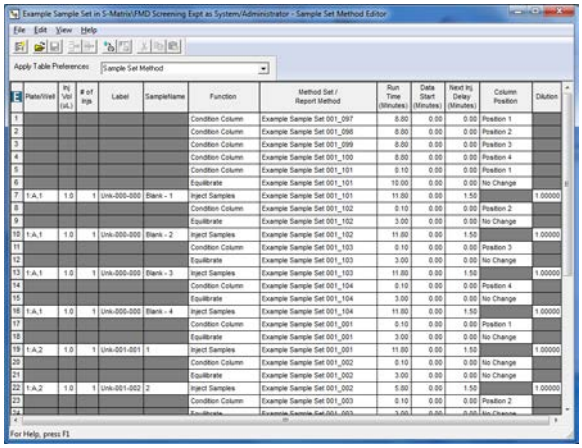
FMD automatically constructs the experiment designs within the CDS as ready-to-run methods and sequences. It also automatically adds column conditioning for each included column to accommodate chemistry system changes between injection (e.g. strong solvent type and/or pH).


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

S-Matrix

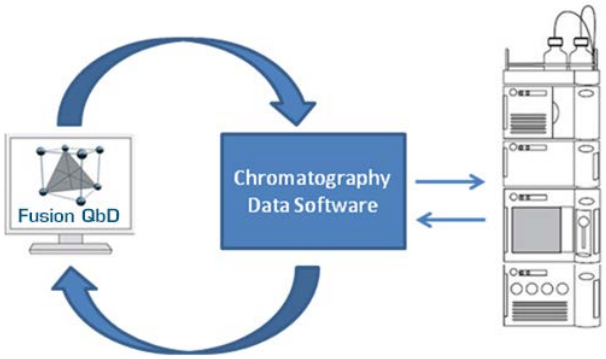
Experiment Design - Experiment 1

Run No.	Sample Set No.	Gradient Time (min)	pH (*)	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	C8
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	C8
8	1	6.0	2.0	C8
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	C8



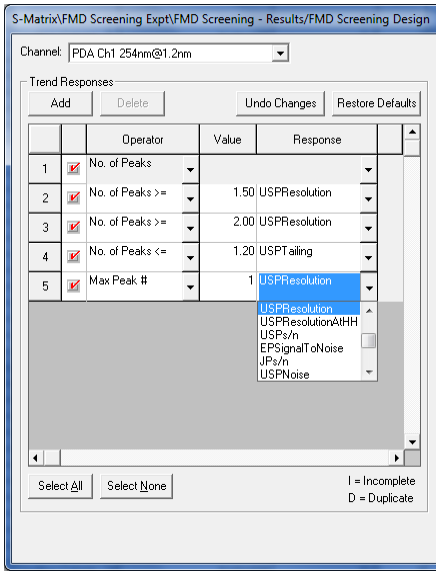
Step 3 – CDS runs the Validation Experiment

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.



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.

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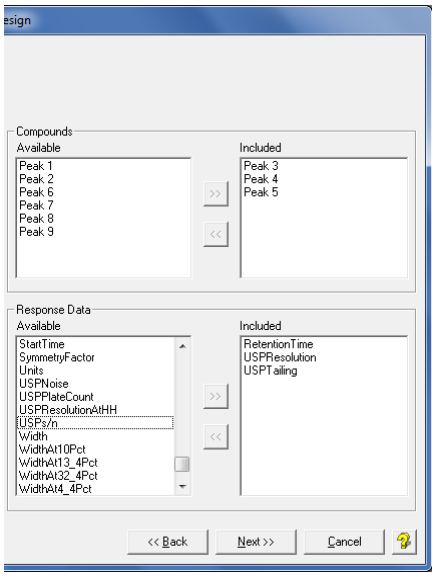
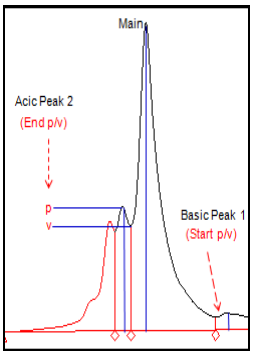
Named Peak Responses – Optimization Experiments



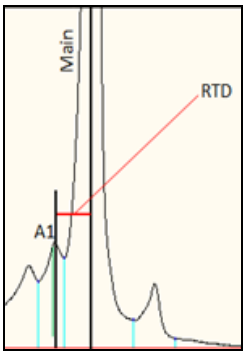
FMD can import and model any results data computed by the CDS for named peaks. You select the results which correspond to your critical method performance characteristics. These are your Critical Quality Attributes (CQA) in QbD terminology!

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).

Peak h/v



RTD



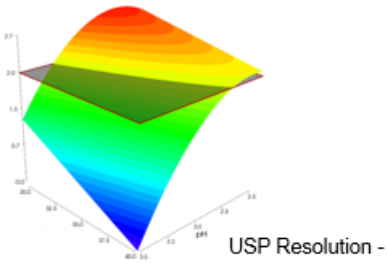
Best Answer Searches

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.

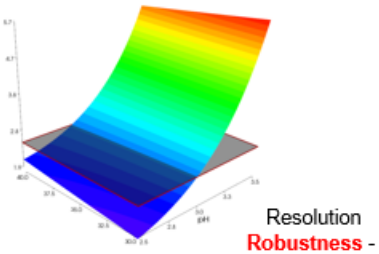
Patented Robustness Simulator™

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.

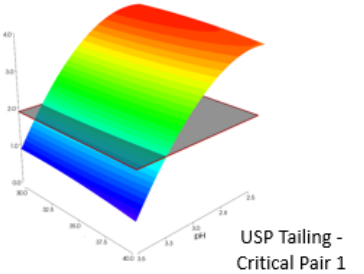
Robustness Simulator uses a correctly-implemented Monte Carlo simulation engine to automatically compute method robustness metrics for all CQAs in your optimization experiment. It graphically shows variable combinations which do not meet mean performance or robustness requirements (shaded regions) –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



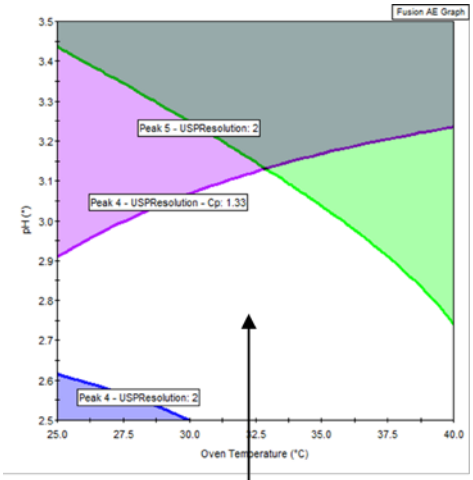
USP Resolution - Critical Pair 1



Resolution **Robustness** - Critical Pair 1



USP Tailing - Critical Pair 1



Design Space –

joint region of acceptable method mean performance and robustness.

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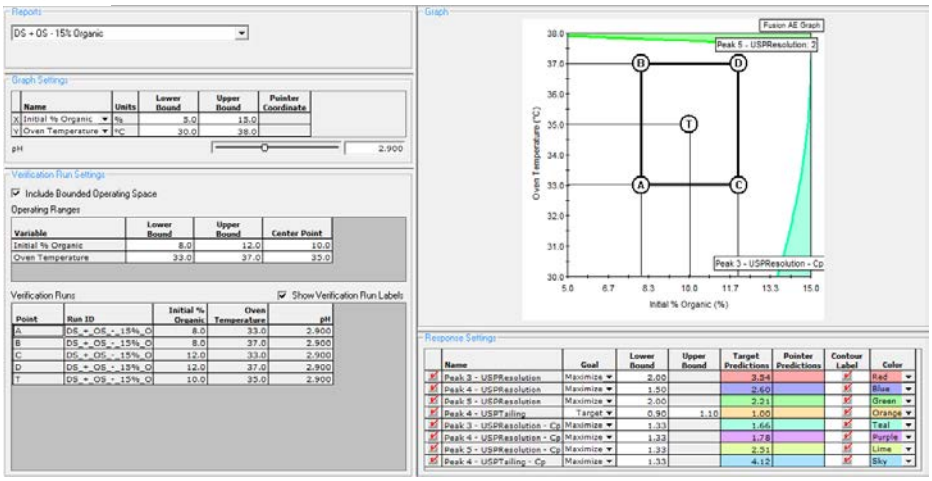
Step 5 – Fusion QbD Automatically Creates Final Reports with QbD Visualization Graphics

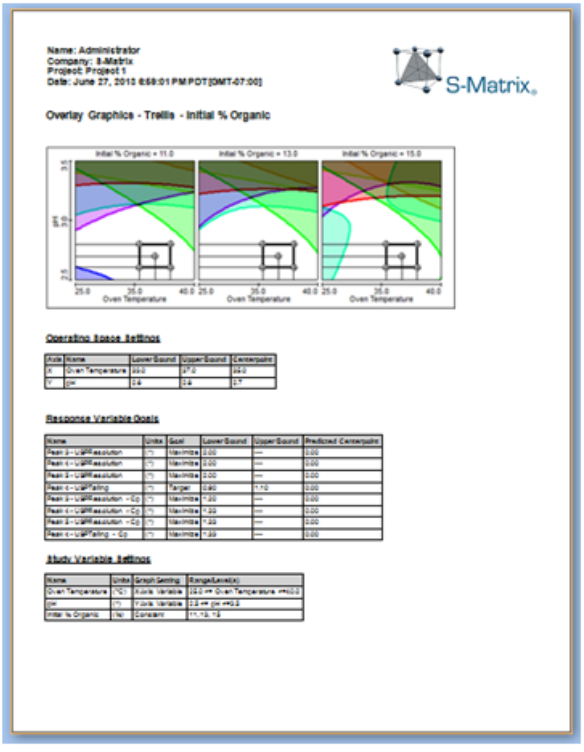
FMD enables you to graphically present your final design space in terms of all your critical method performance attributes (CQAs). A color is assigned to each CQA, and the region of the graph shaded with the color corresponds to methods which do not meet the goal for that CQA.

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.



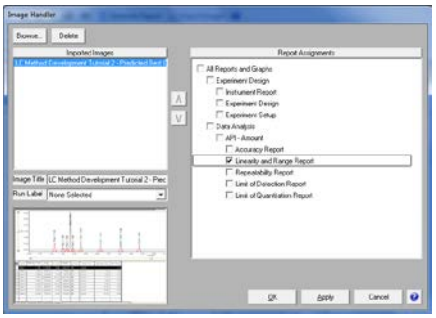
Easily add a graphical display of your Proven Acceptable Ranges (PARs) within your design space.

Here you can dynamically input and update your CQA goals.



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.



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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

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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.

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

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