

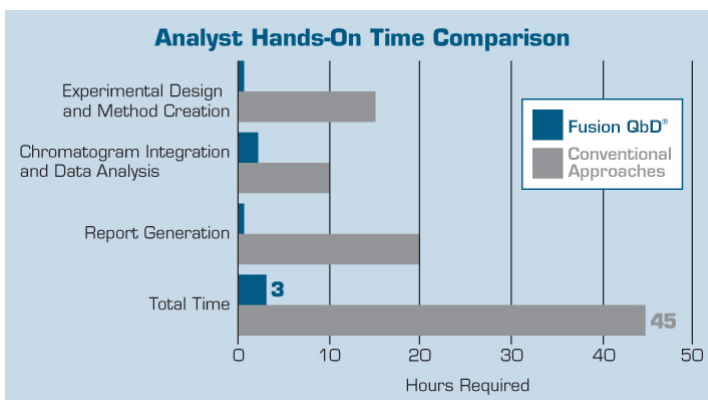
Fusion Method Development

Robust LC and LC/MS 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!
- Dramatically shortens method development time!



Automated • QbD Aligned • LC & LC/MS 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 builds prediction models for all method performance characteristics

➤ Automated Peak Tracking – *Built In!*

Automatically identifies each peak in each experiment chromatogram using PDA and MS Spectral data augmented with standard UV peak results data. Complex separation and tracking challenges PeakTracker can automatically address include:

- Auto-deconvolution of partially and completely co-eluted peaks.
- Two or more peaks with identical mass data.
- Non-ionizing and non-absorbing compounds.

➤ 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 II 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

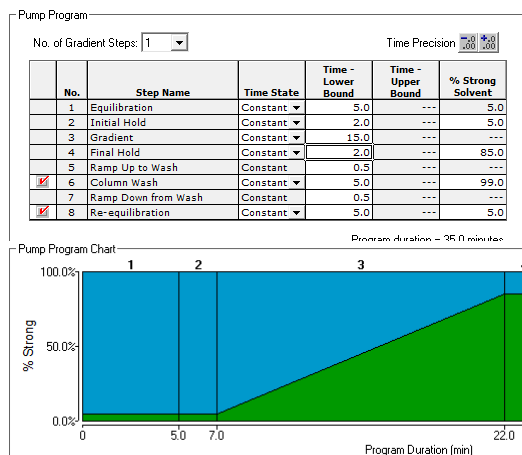
Automated LC Method Development Experimentation – Five Step Workflow

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 Experiment Setup 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



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.

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.

Buffer Selector

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

pH Buffer Settings

No. of Levels: 6

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

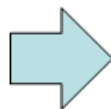
Step 2 – Fusion QbD Generates the Experiment and Exports it to your CDS

FMD automatically builds the experiment 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 and 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 (°)	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	CB
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	CB
8	1	6.0	2.0	CB
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	CB



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

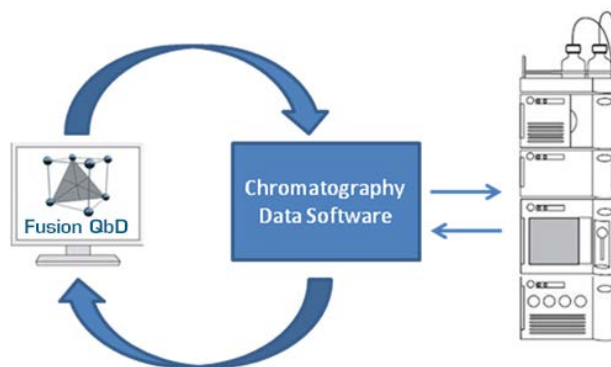
Apply Table Preferences	Sample Set Method	Method Set / Report Method	Run Time (Minutes)	Data Start (Minutes)	Next To Delay (Minutes)	Column Position	Column
1	Phenyl	Condition Column	Example Sample Set 001_097	8.00	0.00	Position 1	
2		Condition Column	Example Sample Set 001_098	8.00	0.00	Position 2	
3		Condition Column	Example Sample Set 001_099	8.00	0.00	Position 3	
4		Condition Column	Example Sample Set 001_100	8.00	0.00	Position 4	
5		Condition Column	Example Sample Set 001_101	9.10	0.00	Position 1	
6		Equilibrate	Example Sample Set 001_101	10.00	0.00	No Change	
7	1.A.1	Inject Samples	Example Sample Set 001_101	11.80	0.00	1.50	1.00000
8		Condition Column	Example Sample Set 001_102	8.10	0.00	Position 2	
9		Equilibrate	Example Sample Set 001_102	3.00	0.00	No Change	
10	1.A.1	Inject Samples	Example Sample Set 001_102	11.80	0.00	1.50	1.00000
11		Condition Column	Example Sample Set 001_103	6.10	0.00	Position 3	
12		Equilibrate	Example Sample Set 001_103	3.00	0.00	No Change	
13	1.A.1	Inject Samples	Example Sample Set 001_103	11.80	0.00	1.50	1.00000
14		Condition Column	Example Sample Set 001_104	5.10	0.00	Position 4	
15		Equilibrate	Example Sample Set 001_104	3.00	0.00	No Change	
16	1.A.1	Inject Samples	Example Sample Set 001_104	11.80	0.00	1.50	1.00000
17		Condition Column	Example Sample Set 001_001	6.10	0.00	Position 1	
18		Equilibrate	Example Sample Set 001_001	3.00	0.00	No Change	
19	1.A.2	Inject Samples	Example Sample Set 001_001	11.80	0.00	1.50	1.00000
20		Condition Column	Example Sample Set 001_002	6.10	0.00	No Change	
21		Equilibrate	Example Sample Set 001_002	3.00	0.00	No Change	
22	1.A.2	Inject Samples	Example Sample Set 001_002	5.80	0.00	1.50	1.00000
23		Condition Column	Example Sample Set 001_003	6.10	0.00	Position 2	
24		Equilibrate	Example Sample Set 001_003	3.00	0.00	No Change	

Step 3 – CDS runs the Experiment

FMD sequences run automatically on the CDS. **FMD** even enables you to include a Shutdown method as the last method run so that you can execute **FMD** sequences overnight while you sleep!

Supported LC Systems Include:

- ChemStation – all Agilent LCs
- Chromeleon – all Thermo Fisher Dionex and Agilent LCs
- Empower – all Waters and Agilent LCs



Step 4 – Fusion QbD Imports and Models the Chromatogram Results

Patented Trend Responses™ – Chemistry Screening Experiments

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 USP Tailing	
5	<input checked="" type="checkbox"/> Max Peak #	1	USPResolution

USPResolution
USPResolutionAHH
USP S/n
EPSignalToNoise
JP S/n
USFNoise

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:

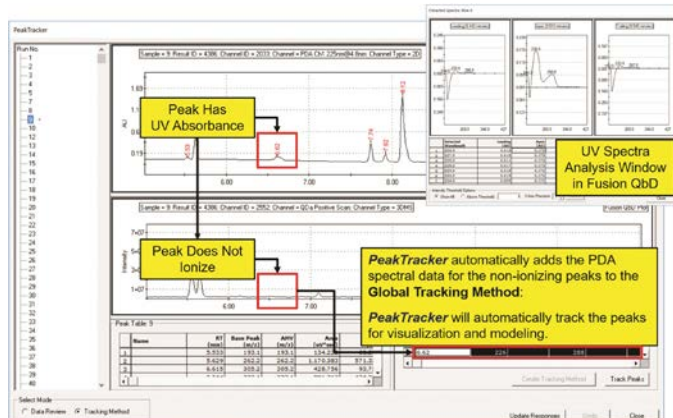
- No. of Integrated Peaks
- No. of Baseline Resolved Peaks
- No. of Peaks with Good Tailing
- No. of Peaks with Specified S/N Ratio

PeakTracker™ – Automated Peak Tracking for Optimization

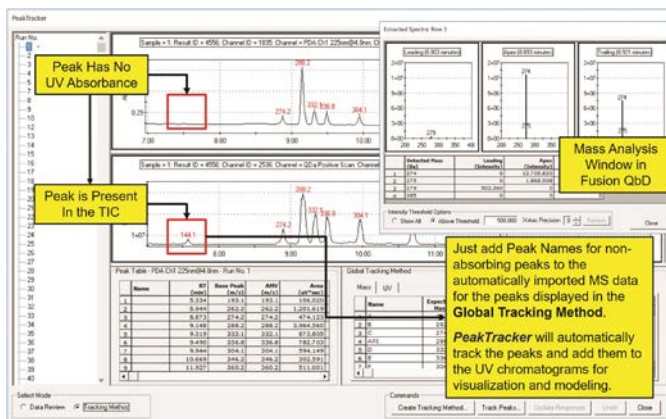
PeakTracker automates and simplifies the use of PDA and MS spectra data in LC and LC/MS method development. PeakTracker uses 3D PDA spectral data augmented with standard UV peak results data to automatically identify each peak in each experiment chromatogram. PeakTracker will also fully utilize 3D mass spectral data for experiments run on LC systems configured with the Waters Acquity QDa Mass Detector (QDa). Complex separation and tracking challenges PeakTracker can automatically address include:

- Auto-deconvolution of partially and completely co-eluted peaks.
- Two or more peaks with identical mass data.
- Non-ionizing and non-absorbing compounds.

Tracks Non-ionizing Peaks



Tracks Non-absorbing Peaks

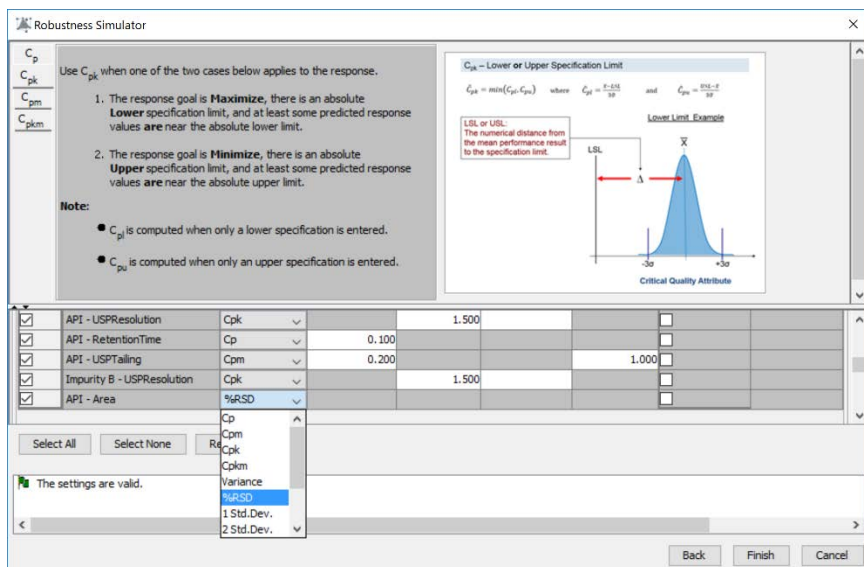


Patented Robustness Simulator™

FMD can automatically import and model all critical method performance 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!

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!

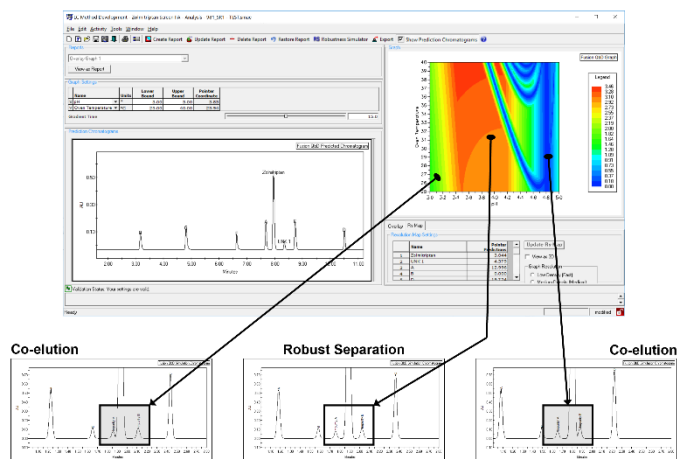


Step 5 – Fusion QbD Automatically Creates Final Reports with QbD Visualization Graphics

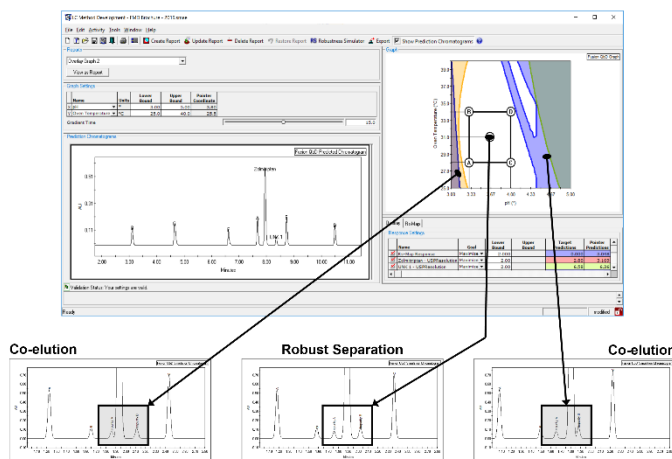
Data Visualization – Rs-Map Response and Multi-Response Overlay modes

You set the required performance goals for all your modeled CQAs. **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.

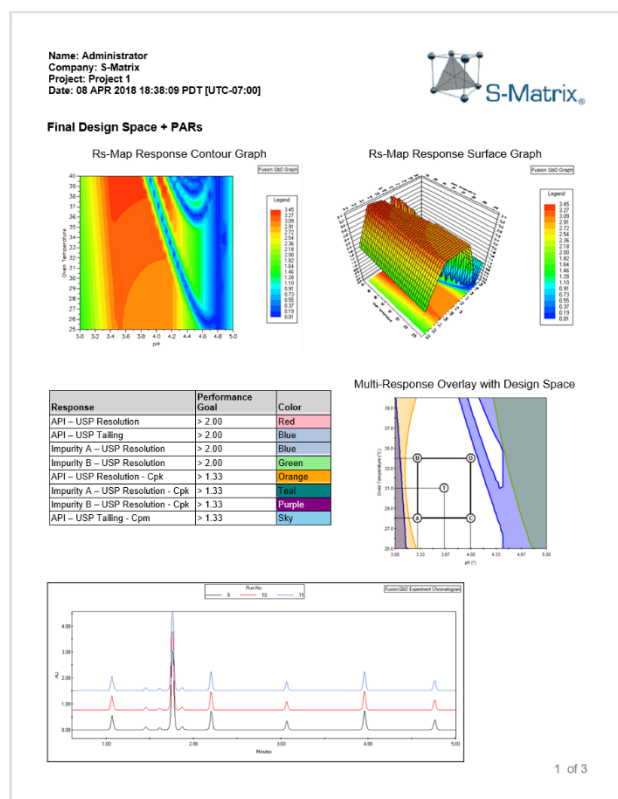
Rs-Map Response Mode



Multi-Response Overlay Mode

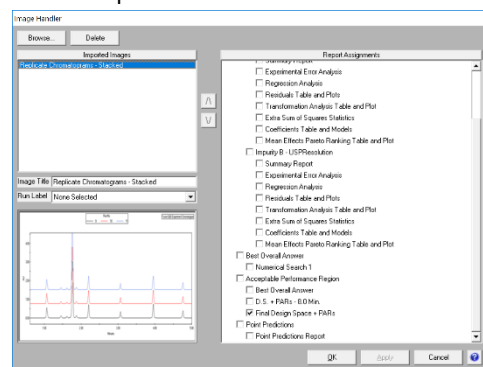


FMD enables you to graphically present your final design space in terms of all your critical method performance attributes (CQAs). A color is assigned to each CQA, and the region of the graph shaded with the color corresponds to methods which do not meet the goal for that CQA.



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

ChemStation CDS

Chromeleon CDS

Empower CDS

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



Chromeleon CDS

Supported Thermo LC Systems

- ✓ Solvent Selection Valves
- ✓ Column Switching Valves

UltiMate LCs



Vanquish Horizon
And Flex LCs



Empower CDS

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 offers interactive web training with a live trainer.

To arrange an on-site or web-based training program, call 707-441-0406.

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