

# Fusion Process Development

Quality by Design Software for  
Formulation & Process Development  
Non-LC Methods Development



# Fusion Process Development

## Quality by Design on a Plate!

If you are wondering where to start when implementing Quality by Design in your organization, Fusion Process Development (**FPD**) is the answer you've been looking for. With automated experimental design selection, validated data exchange, sophisticated data analysis tools, and comprehensive reporting, FPD is the perfect place to start your QbD journey.

### Key Benefits

- Translates QbD Guidances into Usable Tools
- Quantifies and Manages Risk
- Supports 21 CFR Part 11 Compliance
- Designed for Scientists
  - (although statisticians are welcome!)

### Example Applications

- Formulations / Tableting / Coating
- Non-LC Methods Development
  - E.g., Sample Prep., Dissolution, CE, GC, etc.
- Synthetic Chemistry
- Process and Device Development

Systematic, logical, secure and compliant, FPD is perfect for all your development activities, from defining the "Experimental Region" through to reporting the "Operating Space".

### The Experimental Region

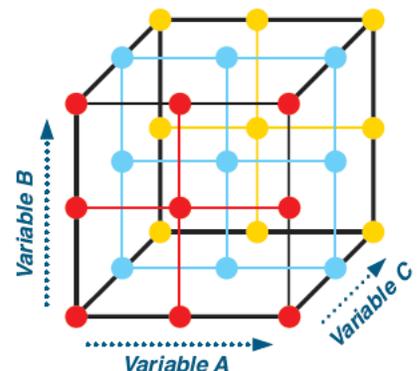
Your journey begins here. **FPD** allows you to define multiple variables (potential Critical Process Parameters) and the ranges over which you wish to study them. It is these that will ultimately define your Knowledge Space.

One key benefit of **FPD** is that you do not need to have a statistics degree to use it! Based on the variable types entered in the Experimental Design template, **FPD** automatically selects the most efficient design suitable for modeling your data, including the higher order models required to visualize complex interaction effects usually responsible for the lack of Robustness.

### Experimental Design

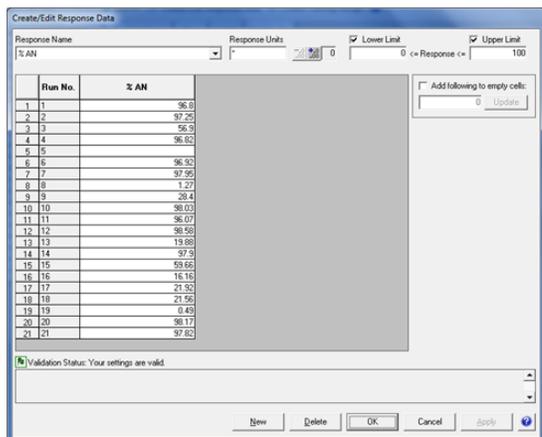
Design of Experiments (DOE) best practices are always adhered to, ensuring that the appropriate number of repeats, center points, and degrees of freedom are used. Designs (the list of experiments to be run) can be exported in a variety of file formats, including MS Excel, Comma or Tab-delimited files, HTML, or XML.

In addition, your departmental statistician can build templates using the "user Interactive" design mode. This enables full control over the choice of design to use and all associated design structure settings. Available design types include: Full and Fractional Factorial, Plackett-Burman, Box-Behnken, Central Composite, Star, Mixed Level, and Model-Robust Algorithm (Letter Optimality) designs.



## Data Management and Processing

Any study is likely to require data from a range of measurement systems to determine the necessary Critical Quality Attribute results. A tablet study for example can generate "basic" Hardness data as well as "complex" Dissolution data. **FPD** supports all these types of data.



### Direct Data Entry

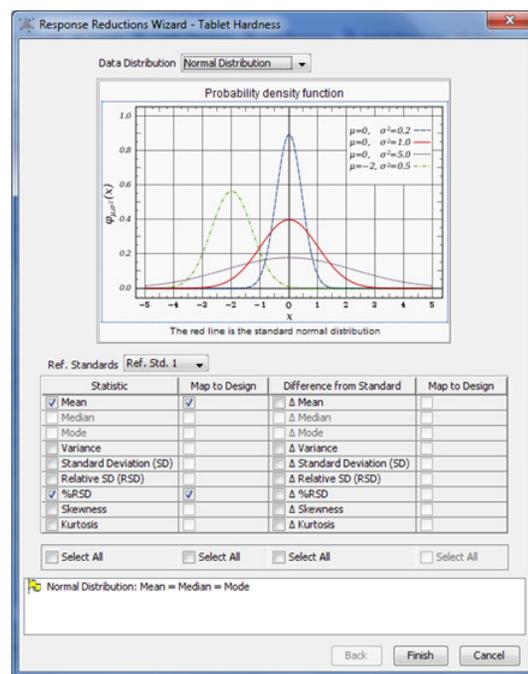
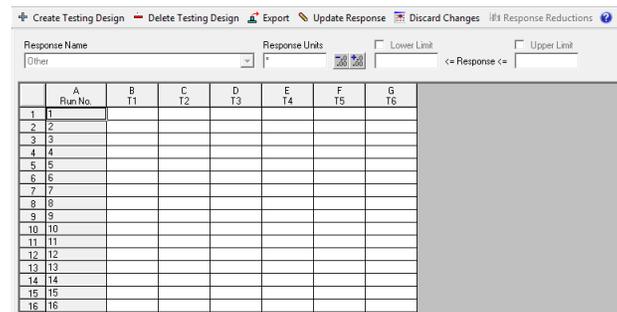
You can directly enter responses consisting of only one measurement per run (no test repeats) as analysis-ready data sets.

For each response you can also enter any limits associated with the test measurement – for example, % Released data for which the measurement cannot exceed 100%. **FPD** will automatically accommodate this critical feature of the response data in its automated data analysis and modeling.

### Testing Plans

Create Testing Plans for response data which consists of multiple test repeats per experiment run (test replicates).

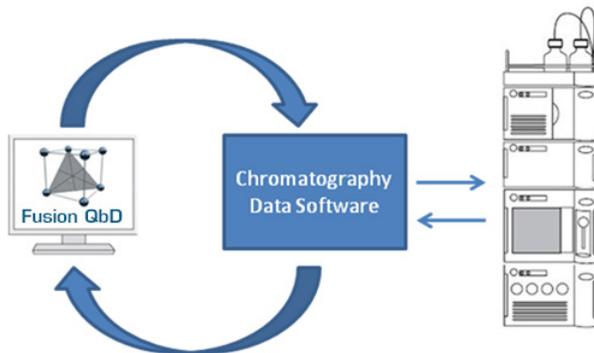
**FPD** will automatically translate your test repeat data into any statistical result you want to analyze, such as Mean, Variance, Std. Dev., % RSD, etc. And **FPD** can handle non-normally distributed test data.



## Chromatography Interfaces

**FPD** automatically exchanges testing plans and chromatogram results with Chromatography Data Software via validated and fully audited processes.

**FPD** both builds the sequences/sample sets to be run, and extracts the required peak result data to populate the target "Testing Plan". This is a key feature ensuring quality, as transcription error is a common source of bad data that results in poor models.

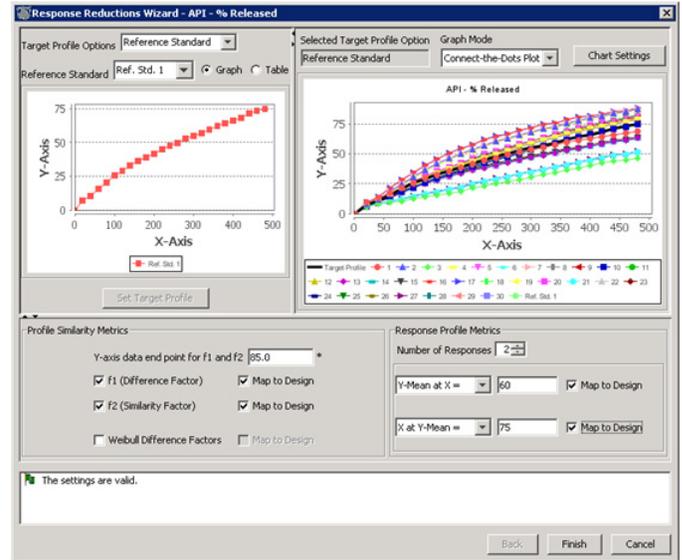


## Time Series Toolset

With this toolset you can create Testing Plans for "complex" time series profile data such as are obtained from dissolution testing and synthesis reaction testing.

Time Series Toolset can automatically:

- handle test repeat data at each testing time point
- compute response profiles
- compute f1 & f2 curve fit metrics
- run guidance specified f1 & f2 data quality checks
- compute sensitive Weibull curve fit metrics
- compute additional profile response metrics such as the mean response at a given test time point, or the time point associated with the given test result
- map all computed responses to the experimental design for automated data analysis



## Inhaler Testing Toolset

With this toolset you can create Testing Plans for respiratory drug and device testing results data such as are obtained from ACI and NGI cascade impactor testing.

The Inhaler Testing Toolset can automatically create Testing Plans for:

- USP Apparatus I-6 and Ph.Eur. 2.9.18 Apparatus C, D, E.
- any combination of device by stage of dose delivery life

The Inhaler Testing Toolset can also automatically:

- compute apparatus stage and group averages, Material Balance, Mass Balance, Metered Dose, Emitted Dose, Actuator/Device Retention, Fine Particle Dose (FPD), Fine Particle Fraction (FPF), Mass Median Aerodynamic Diameter (MMAD), and Geometric Standard Deviation (GSD)
- map all computed responses to the experimental design for automated data analysis

Actuation Settings

Total Number of Actuations (shots) per Test

Number of Actuations (shots) per Dose

Nesting Hierarchy

Tier 1  Tier 2

Stage of Life Settings

No. of Stages

Block on Stage of Life

Device Settings

No. of Devices

Block on Device

Stage of Dose Delivery Life	Device ID
1-5	Device 1
101-105	Device 1
196-200	Device 1

Material/Mass Balance

Report Material/Mass Balance Uniformity Spec. +/-  %

Optional Groups by Stage

Group Name	From Stage	To Stage
1. Stage Group 1	Device	MDC
2. Stage Group 2	Device	MDC

Device Retention

Optional Group Calculations

Group Calculation	Group Name	Group Weight	Group Retention	Group Fraction
<input checked="" type="checkbox"/>				

Optional Groups by Particle Size

Group Name	Minimum	Maximum	Calculation Method
1. Size Group 1	5.0000	8.0000	Regression
2. Size Group 2	0.0000	5.0000	Regression

Regression Settings

Standard  Custom

Lower Bound %  Upper Bound %

Linearity Range

R-square Value

Fine Particle Mass (FPM)

Determination Method

Apparatus Stage  From Stage  To Stage

Particle Size

Upper Limit <=  um

Calculation Method

Interpolation  Regression

Regression Settings

Standard  Custom

Lower Bound %  Upper Bound %

Linearity Range

R-square Value

Prediction Limits +/-  Sigma

Fine Particle Fraction (FPF)

Determination Method

Apparatus Stage  From Stage  To Stage

Delivered Dose Uniformity

Fine Particle Mass

Delivered Dose Uniformity

MMAD

MMAD (Mass Median Aerodynamic Diameter)

Interpolation  Regression

GSD

GSD (Geometric Standard Deviation)

Interpolation  Regression

Regression Settings

Standard  Custom

Lower Bound %  Upper Bound %

Linearity Range

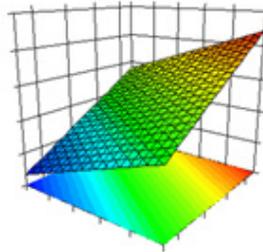
R-square Value

## Knowledge Space

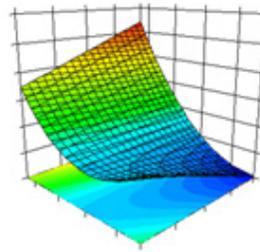
With your rationalized experimental data mapped to the design, the data analysis can begin. With a click of a button

FPD will perform your multi-variant analysis and build the empirical models describing the relationships between your potential Critical Process Parameters (CPPs) and Critical Quality Attributes (CQAs). These are displayed as readily interpretable Response Surfaces, contour plots and effects plots ensuring you acquire "formulation and process understanding".

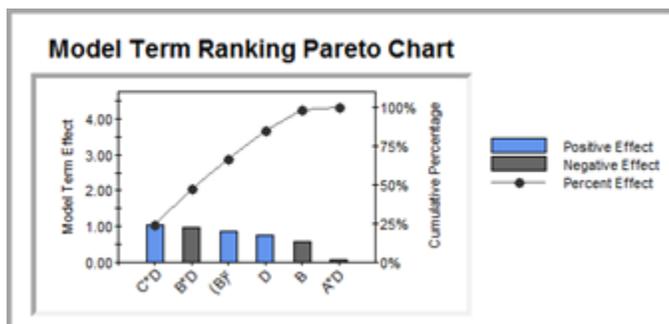
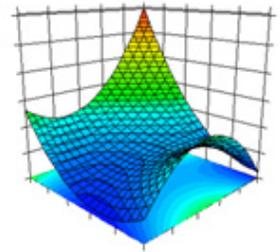
Independent Linear Effects



Interaction Effects



Complex Effects



Pareto Ranking charts allow you to see which study variables should be treated as Critical Process Parameters.

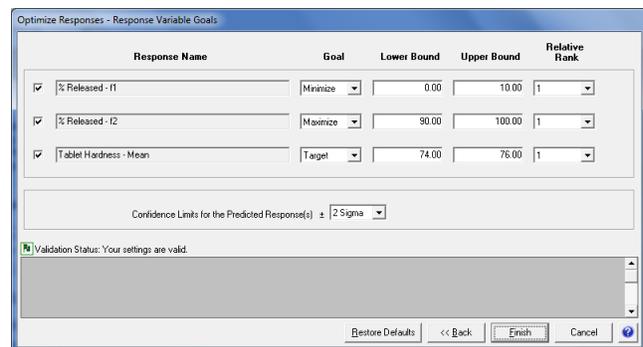
Analysis Summary and Detail Reports define the quality of your experimental data, allowing you to have confidence in the models generated.

## Best Overall Answer

With your Knowledge Space established, FPD's powerful Numerical Best Answer Search tool allows you to search for the conditions that meet all your required Critical Quality Attribute goals. Results are produced and displayed in concise tabular and graphical report formats.

### Study Variable Data

Study Variable	Optimizer Answer
Atomizing Air Pressure	10.0
Pattern Air Pressure	55.0
Spray Rate	40.0
Gun-to-Bed Distance	8.9



Numerical Best Answer Search reporting displays the "Best Result" level setting of each experiment variable, and also reports the level settings of all key factors maintained constant for the experiment.

### Predicted Response Data

Response	Target	Optimizer Answer Predicted Response	-2 Sigma Confidence Limit	+2 Sigma Confidence Limit
% Released - f1	Minimize	0.6185	0.2289	1.4887
% Released - f2	Maximize	95.2426	92.7147	97.7704
Tablet Hardness - Mean	75.0	74.8363	74.6912	74.9815

Desirability Target = 1.0000  
Desirability Result = 0.7439

Numerical Best Answer Search reporting also includes the model-predicted result for each included response (CQA), along with the prediction confidence interval limits, and the "Overall Desirability" of the results relative to all your goals.

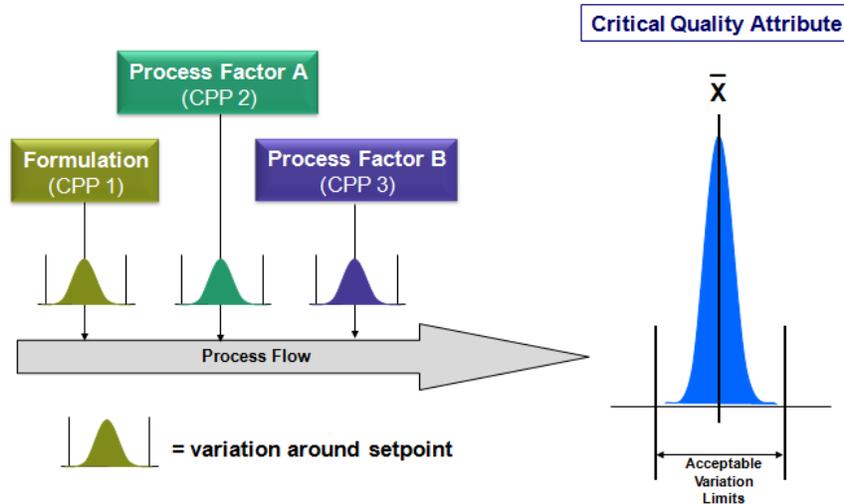
## Quantification of Risk – Formulation & Process Robustness

### Robustness

*"Ability of a process to tolerate variability of materials and changes of the process and equipment without negative impact on quality."*

Fusion QbD's patented Robustness Simulator™ technology (U.S. Patent No. 7,606,685 B2) allows you to quantify risk. Enter expected variation in your Critical Process Parameters (CPPs) and allowable variation limits for your Critical Quality Attributes (CQAs).

Fusion QbD will automatically compute and model Robustness metrics (Process Capability metrics – e.g.  $C_p$ ,  $C_{pk}$ ), enabling you to characterize Robustness and incorporate that characterization into your Knowledge Space and Design Space (or Method Operable Design Region – MDDR).



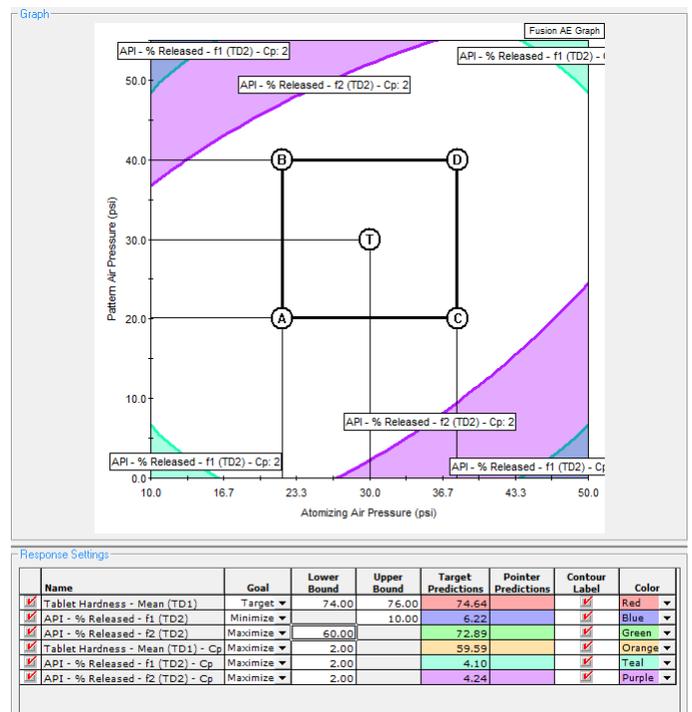
### Design Space

*"The multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality."*

### Independently Adjustable Ranges Rectangle

Overlay a rectangle defining the independently adjustable ranges of the graphed variables. The rectangle within the MDDR demarcates the ranges within which you can independently adjust the graphed variable's method setpoints without fully revalidating the method. The rectangle represents a regular geometry – meaning straight-line borders. When the entire region within the rectangle is unshaded, then the graphed variables can be independently adjusted to correct for drifts toward unacceptable performance.

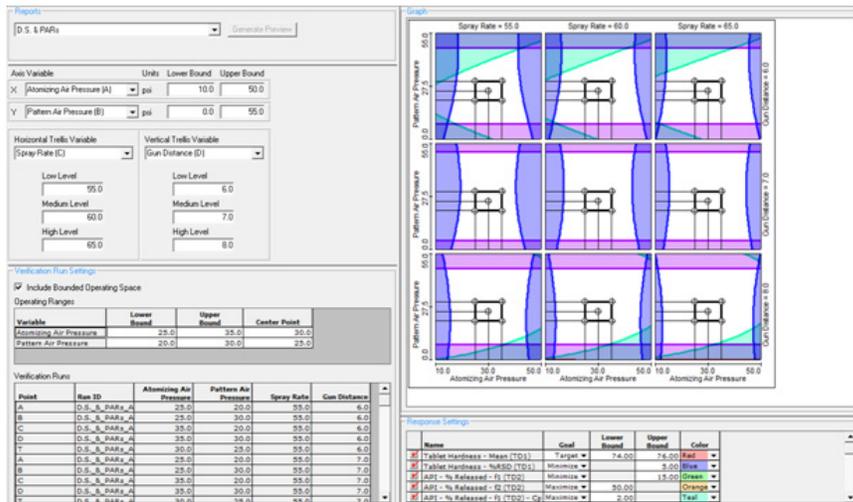
Visualization feature assigns a color to each response, and then uses the color to shade the region of unacceptable performance for the response. The **UN-shaded** region thus represents the region of acceptable performance for the response. As many responses as desired can be included in a graph, so that the un-shaded region represents the robust Design Space for all included responses.



## Visualize and Report – Formulation/Process Design Space or MDDR

Color-coded response maps define the QbD Knowledge and Design Spaces. Users can predict and display best and most robust conditions.

FPD enables you to scribe the Quality-by-Design (QbD) “operating space” – the specified optimal conditions and the control limits of the critical parameters being studied – on the Design Space graphs. The specified conditions and limits which define the operating space are automatically added to the output reports.



## Scalable from Walk-up System to Global Enterprise Solution

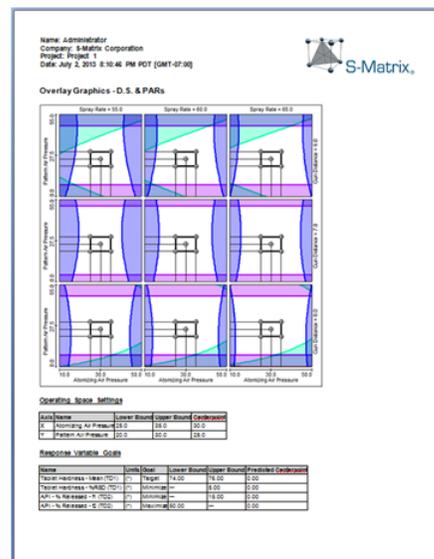
### Fusion Process Development

- Workstation (Standalone) Version
- Network Version – Certified Citrix Ready
- Full Part II Compliance Support / Workflow Management System
- Data Exchange with Chromatography Data Software

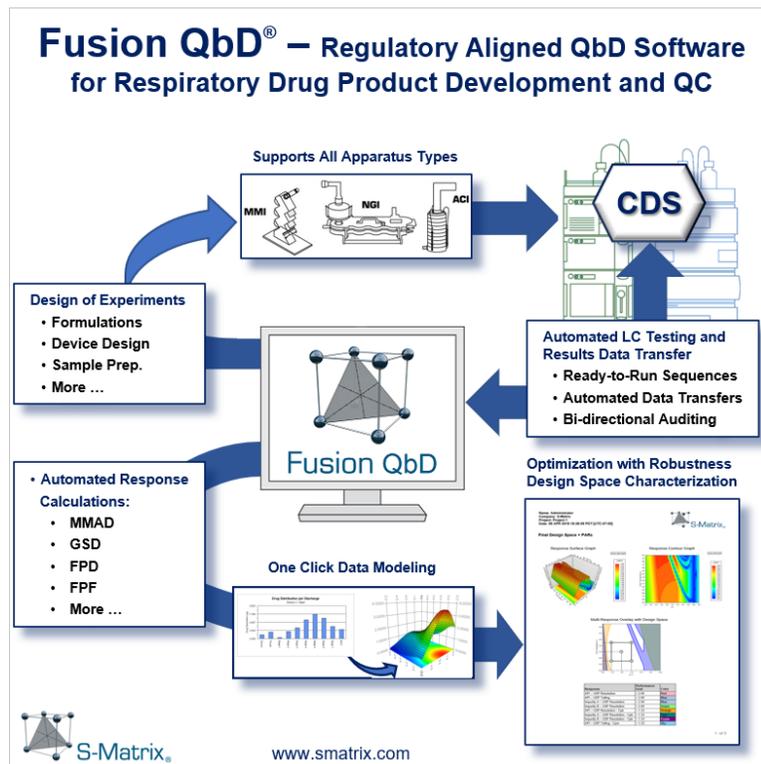
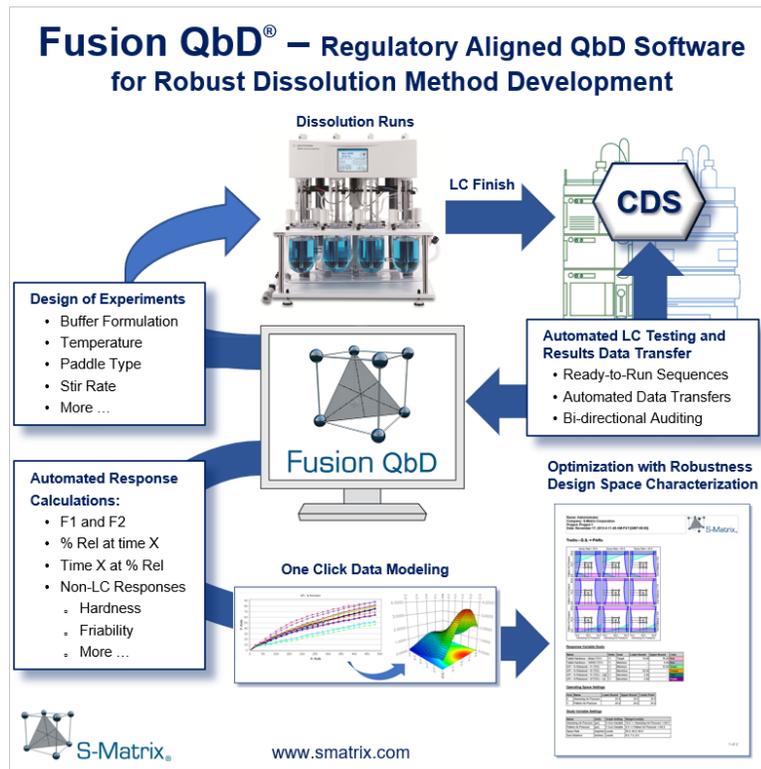


## Fusion Process Development – Science at its best!

- Walks the scientist through the QbD maze
- Ensures QbD “best practices” are followed
- Automates design selection, data transfer and analysis, optimization, and reporting
- Outputs reports in a variety of file formats, including MS Word, HTML, and PDF
- Scales from a single PC to corporate networks, supporting VMware and Citrix environments
- Designed for cGXP and 21 CFR Part II environments



# Example Workflows for Non-LC Methods Development



# S-Matrix Software Products and Support

S-Matrix Corporation develops advanced Design of Experiment based-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 Process R&D.

## Fusion QbD Software System Product Suite

- ◆ **Fusion 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 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 Process Development**  
The perfect QbD software for formulation & process development – automated experimental design selection, sophisticated analysis tools, including automated modeling and simulation, comprehensive reporting, with a full 21 CFR 11 compliance toolset.
- ◆ **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.

## 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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