S-Matrix®

Fusion QbD

Fusion Process Development Module

S-Matrix Corporation

www.smatrix.com

Key Benefits of Fusion Process Development

- Supports All Install Environments (Citrix Ready Certified) ✓
- Full 21 CFR Part 11 Compliance Support ✓
- Flexible, Automated (1-Click) Design ✓
- Full LC Testing Automation ✓
- Simplifies Handling of Complex Data ✓
- Integrated Monte Carlo Robustness ✓
- Full QbD Reporting ✓

Example Applications and Workflows

Example Applications

- Tablet Coating Optimization
- Tablet Excipient Formulation and Process Optimization

Example Workflows

- Sample Preparation Method Development
- Dissolution Method Development
- Respiratory Drug Development

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Supports All Install Environments

Install Environment	FPD
Standalone (Workstation)	✓
Network (Enterprise)	✓
Citrix Ready Certified	✓
Fully Qualifiable for GXP Environments*	✓

* – Fusion QbD is operating in the GxP environments of international pharmaceutical companies worldwide.

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Full 21 CFR Part 11 Compliance Support

How Fusion Process Development Assures Compliance

Required Features	FPD
Full integration of **all e-record** and **all e-signature** features and functions required to support full 21 CFR 11 compliance.	✓
Integrated Project Management System.	✓
Full audit trail, including all data exchanges with the CDS.	✓

Full 21 CFR Part 11 Compliance Support

Why Compliance is Important!

FDA Statement Regarding Robustness Done During Method Development* –

As long as the **data integrity** associated with the method development work matches what would be done in a formal Validation Robustness effort, then the results are acceptable.

Same Regulatory Expectation for Claims of Formulation and Process Robustness

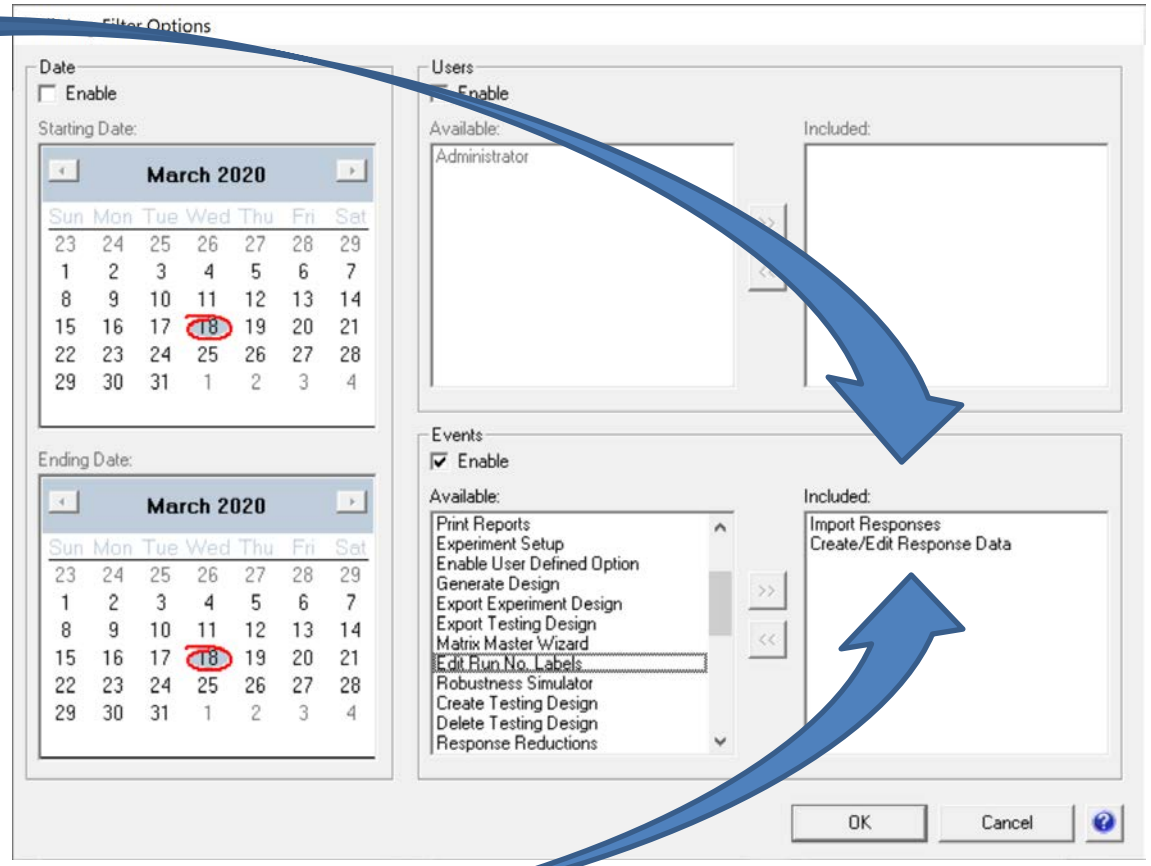
* – USP Workshop – Enhanced Approaches for Analytical Procedure Lifecycle: An Alternative to Traditional Validation (Sept. 24-25, 2018)

Full 21 CFR Part 11 Compliance Support

Why Audit Trail is Important!

What CDS Project did this data come from?

Who entered this data – was the data modified?



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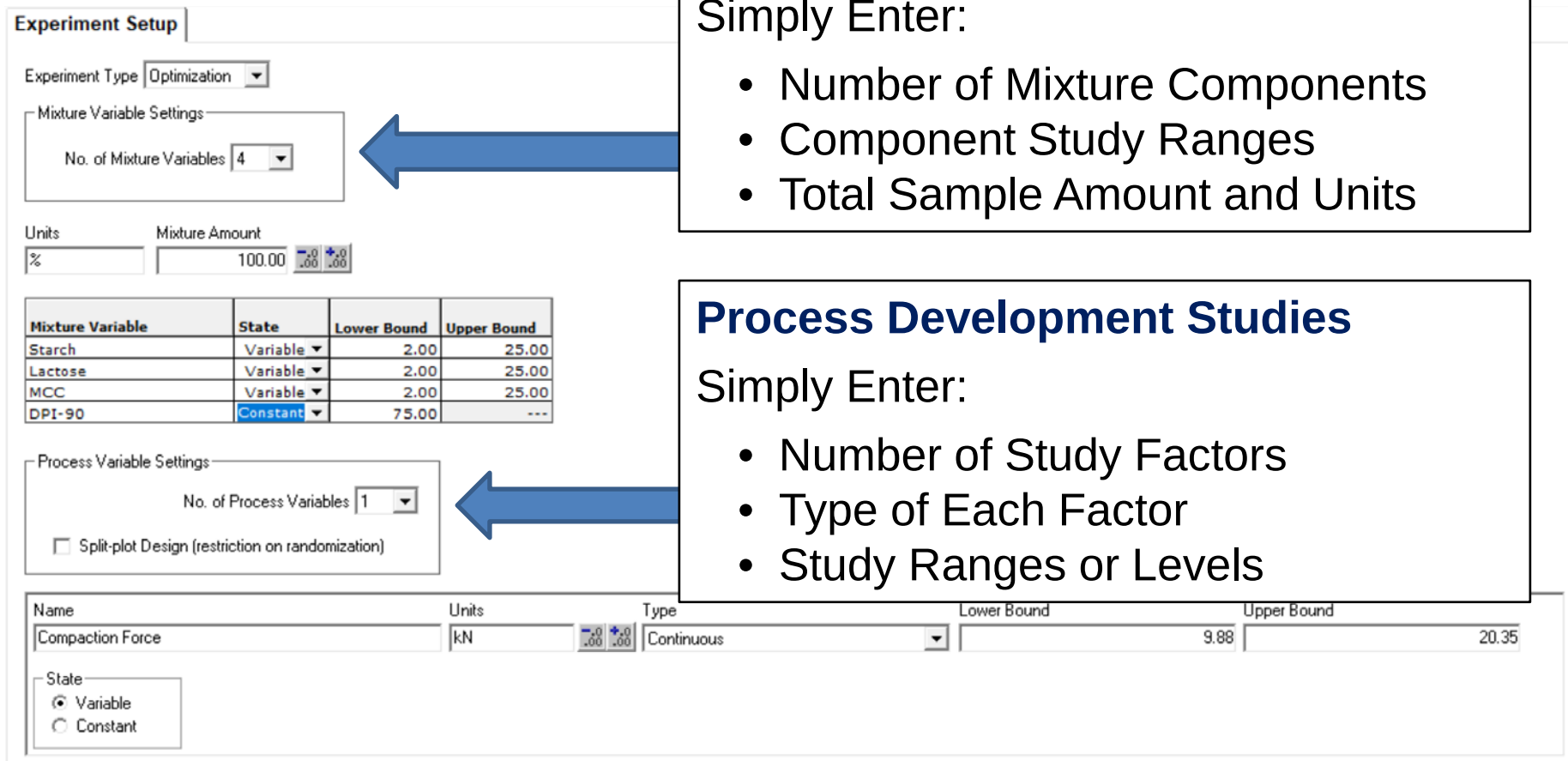
Flexible Experiment Design – Easy Setup



Formulation (Mixture) Studies

Simply Enter:

- Number of Mixture Components
- Component Study Ranges
- Total Sample Amount and Units

Process Development Studies

Simply Enter:

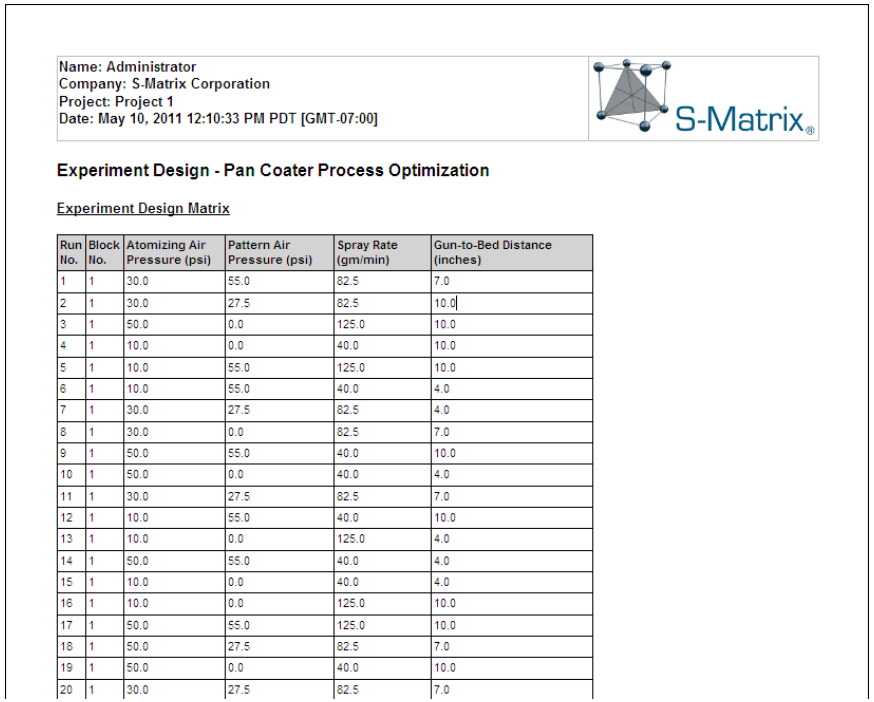
- Number of Study Factors
- Type of Each Factor
- Study Ranges or Levels

Combined Mixture-Process Studies

Enables you to characterize interactions between the two!

Automated Design Wizard Mode – 1-Click

Automated DOE Wizard Selects and Generates the Right Design for you!



Name: Administrator
Company: S-Matrix Corporation
Project: Project 1
Date: May 10, 2011 12:10:33 PM PDT [GMT-07:00]

Experiment Design - Pan Coater Process Optimization

Experiment Design Matrix

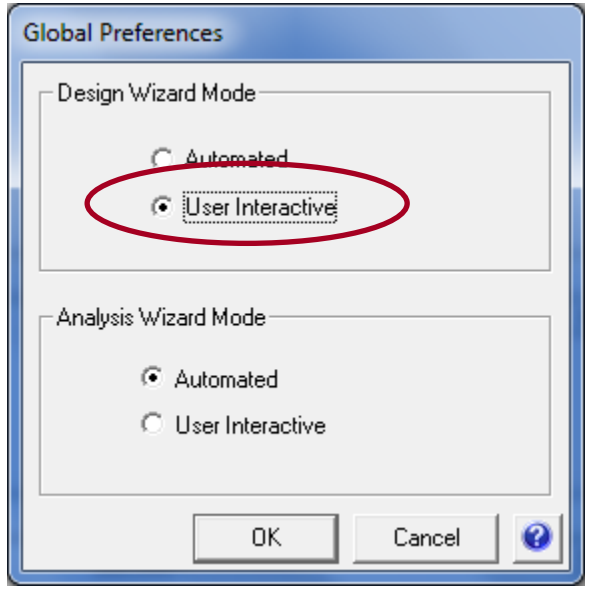
Run No.	Block No.	Atomizing Air Pressure (psi)	Pattern Air Pressure (psi)	Spray Rate (gm/min)	Gun-to-Bed Distance (inches)
1	1	30.0	55.0	82.5	7.0
2	1	30.0	27.5	82.5	10.0
3	1	50.0	0.0	125.0	10.0
4	1	10.0	0.0	40.0	10.0
5	1	10.0	55.0	125.0	10.0
6	1	10.0	55.0	40.0	4.0
7	1	30.0	27.5	82.5	4.0
8	1	30.0	0.0	82.5	7.0
9	1	50.0	55.0	40.0	10.0
10	1	50.0	0.0	40.0	4.0
11	1	30.0	27.5	82.5	7.0
12	1	10.0	55.0	40.0	10.0
13	1	10.0	0.0	125.0	4.0
14	1	50.0	55.0	40.0	4.0
15	1	10.0	0.0	40.0	4.0
16	1	10.0	0.0	125.0	10.0
17	1	50.0	55.0	125.0	10.0
18	1	50.0	27.5	82.5	7.0
19	1	50.0	0.0	40.0	10.0
20	1	30.0	27.5	82.5	7.0

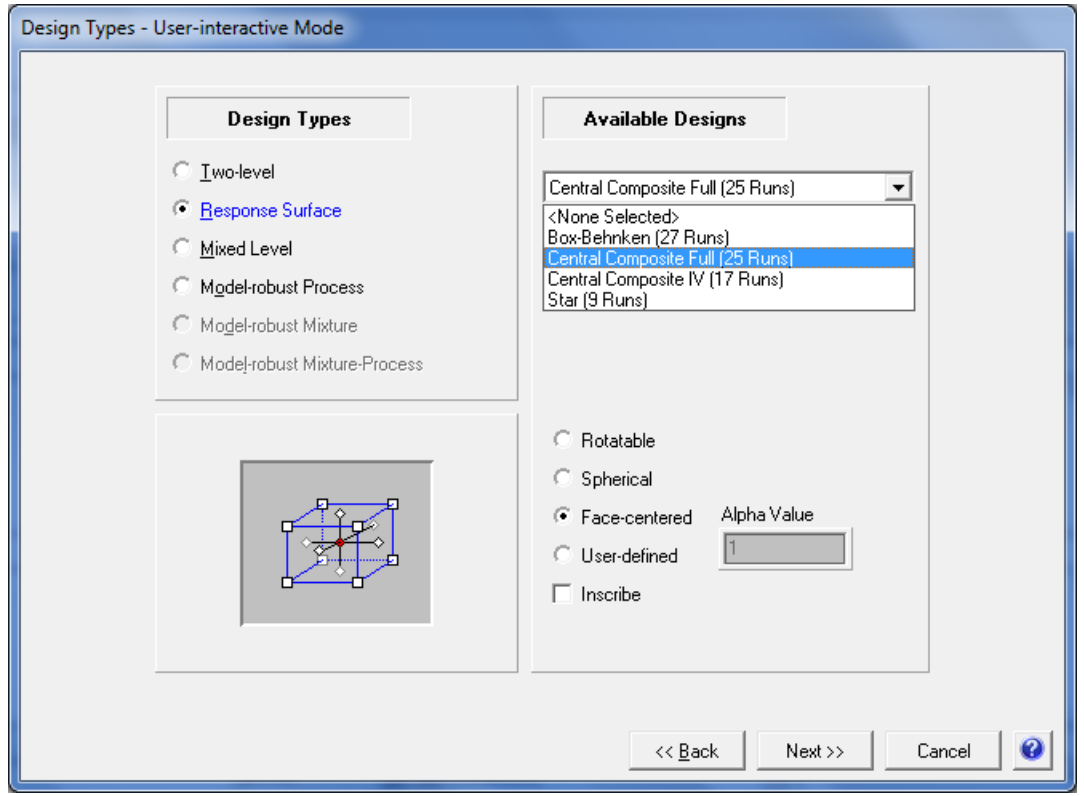
Automated Design Logic Accounts for:

- **Stage of the Work**
  (Screening or Optimization)
- **Number of Variables**
- **Types of Variables**
  Continuous Numeric
  Discrete Numeric
  – # of defined levels
  Categorical (Non-numeric)
  – # of defined levels

User Interactive Design Wizard Mode

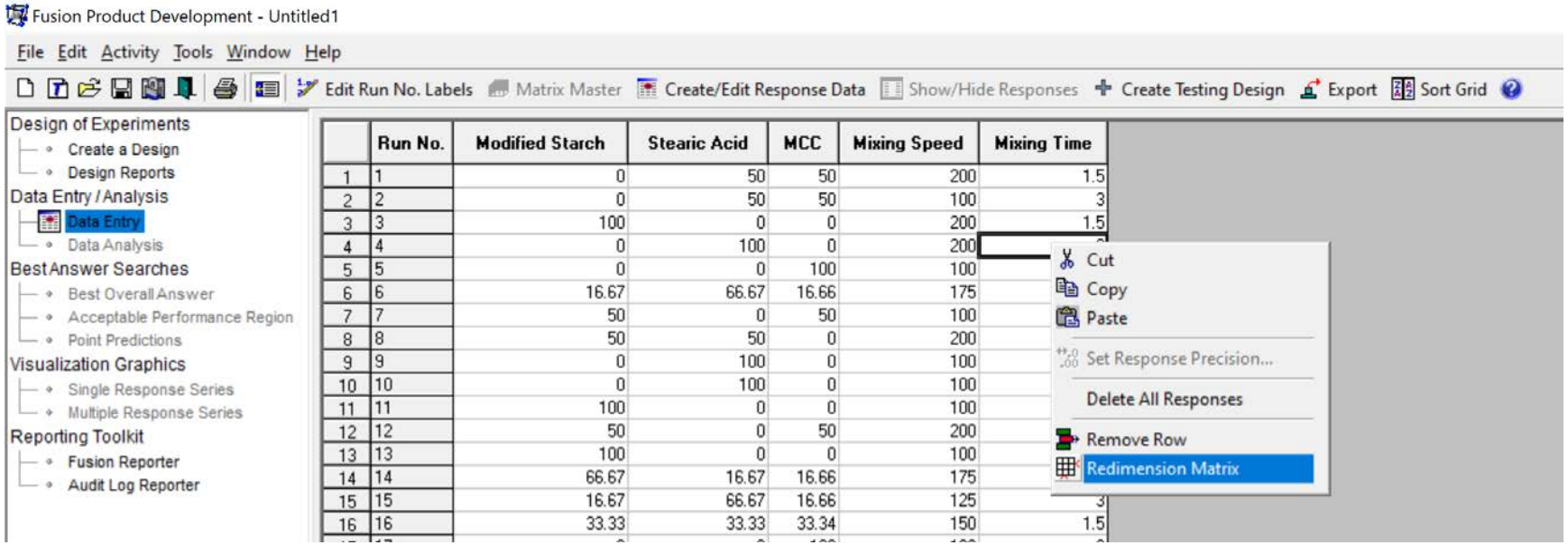
- **DOE Expert Users**
- **Users Following an SOP**





Flexible Experiment Design

Can Accept Designs and Results from Other Software



	Run No.	Modified Starch	Stearic Acid	MCC	Mixing Speed	Mixing Time
1	1	0	50	50	200	1.5
2	2	0	50	50	100	3
3	3	100	0	0	200	1.5
4	4	0	100	0	200	
5	5	0	0	100	100	
6	6	16.67	66.67	16.66	175	
7	7	50	0	50	100	
8	8	50	50	0	200	
9	9	0	100	0	100	
10	10	0	100	0	100	
11	11	100	0	0	100	
12	12	50	0	50	200	
13	13	100	0	0	100	
14	14	66.67	16.67	16.66	175	
15	15	16.67	66.67	16.66	125	3
16	16	33.33	33.33	33.34	150	1.5

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- **Full LC Testing Automation** ✓
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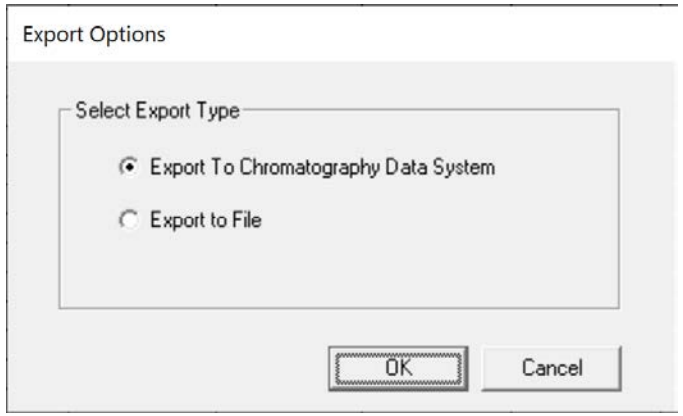
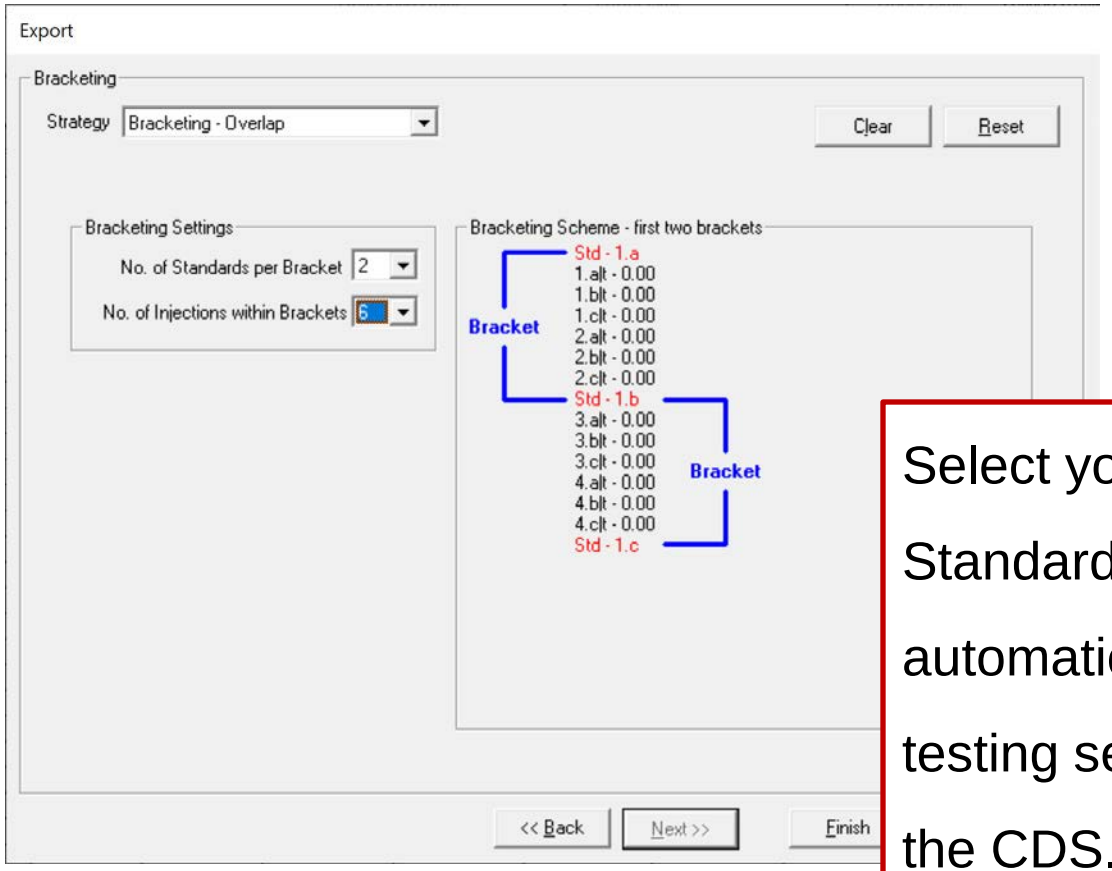
- Integrated Monte Carlo Robustness ✓
- Full QbD Reporting ✓

Export Testing Design Sequences to the CDS

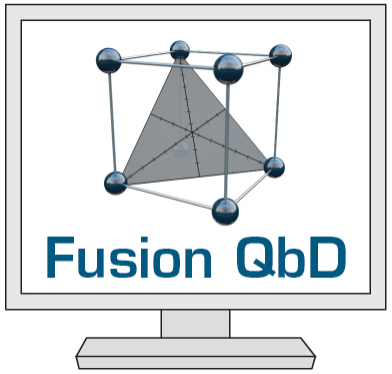
Standards Protocol Setup Wizard





Select your standards protocol – Standard injections are automatically included in the testing sequence exported to the CDS.

Export Testing Design Sequences to the CDS



Generates QbD-aligned DOE Experiment

Automatically Builds Testing Sequence as Ready-to-Run

Fusion QbD automatically builds testing sequences in your CDS which can include your standard injection protocol for all test data which will be generated by LC testing.

Chromatography Data Software (CDS)

Text Mix pH in S-Matrix - MD Demo\LC Tutorial - Sample Workup as System/Administrator - Sample Set Method Editor

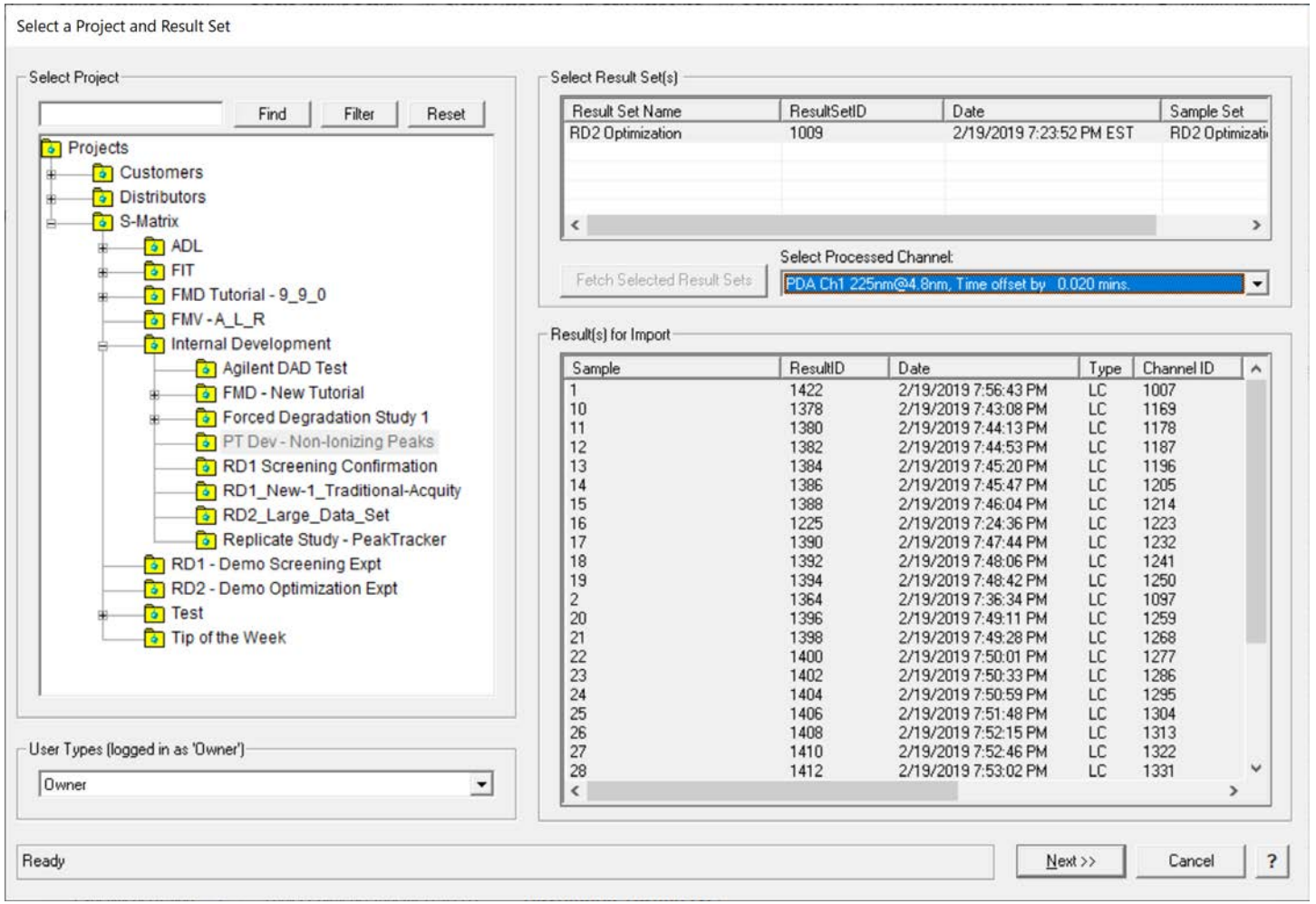
File Edit View Help

Apply Table Preferences | Sample Set Method

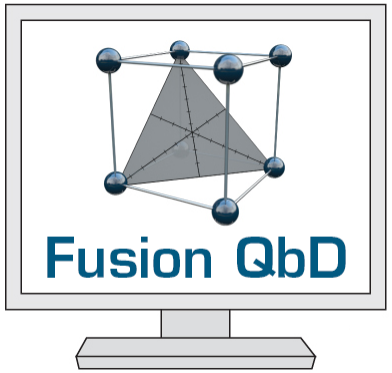
	Vial	Inj Vol (uL)	# of Injs	Label	SampleName	Level	Function	Method Set / Report Method	Label Reference	Processing	Run Time (Minutes)	Data Start (Minutes)	Next Inj. Delay (Minutes)	Column Position	Auto Additions	SampleWeight	Dilution
1							Condition Column				6.70	0.00	0.00	No Change			
2							Condition Column	Text Mix pH 001_017			0.10	0.00	0.00	No Change			
3							Equilibrate	Text Mix pH 001_017			3.00	0.00	7.95	No Change			
4	1	2.0	1	Unk-000-000	Blank - 1		Inject Samples	Text Mix pH 001_017		Normal	10.50	0.00	1.50			1.00000	1.00000
5							Condition Column	Text Mix pH 001_001			0.10	0.00	0.00	No Change			
6							Equilibrate	Text Mix pH 001_001			3.00	0.00	0.00	No Change			
7	2	2.0	1	Unk-001-001	1.a.1.a		Inject Samples	Text Mix pH 001_001		Normal	10.50	0.00	1.50			1.00000	1.00000
8							Condition Column	Text Mix pH 001_002			0.10	0.00	0.00	No Change			
9							Equilibrate	Text Mix pH 001_002			3.00	0.00	0.00	No Change			
10	2	2.0	1	Unk-001-002	2.a.1.a		Inject Samples	Text Mix pH 001_002		Normal	10.50	0.00	1.50			1.00000	1.00000
11							Condition Column				6.70	0.00	0.00	No Change			
12							Condition Column	Text Mix pH 001_003			0.10	0.00	0.00	No Change			
13							Equilibrate	Text Mix pH 001_003			3.00	0.00	0.00	No Change			
14	2	2.0	1	Unk-001-003	3.a.1.a		Inject Samples	Text Mix pH 001_003		Normal	10.50	0.00	1.50			1.00000	1.00000
15							Condition Column				6.70	0.00	0.00	No Change			
16							Condition Column	Text Mix pH 001_004			0.10	0.00	0.00	No Change			
17							Equilibrate	Text Mix pH 001_004			3.00	0.00	0.00	No Change			
18	2	2.0	1	Unk-001-004	4.a.1.a		Inject Samples	Text Mix pH 001_004		Normal	10.50	0.00	1.50			1.00000	1.00000
19							Condition Column	Text Mix pH 001_005			0.10	0.00	0.00	No Change			
20							Equilibrate	Text Mix pH 001_005			3.00	0.00	0.00	No Change			
21	2	2.0	1	Unk-001-005	5.a.1.a		Inject Samples	Text Mix pH 001_005		Normal	10.50	0.00	1.50			1.00000	1.00000
22							Condition Column				6.70	0.00	0.00	No Change			
23							Condition Column	Text Mix pH 001_006			0.10	0.00	0.00	No Change			
24							Equilibrate	Text Mix pH 001_006			3.00	0.00	0.00	No Change			

Automated, Audited Data Exchange Preserves Data Integrity

Import All Required Results Data from CDS



Import All Required Results Data from CDS



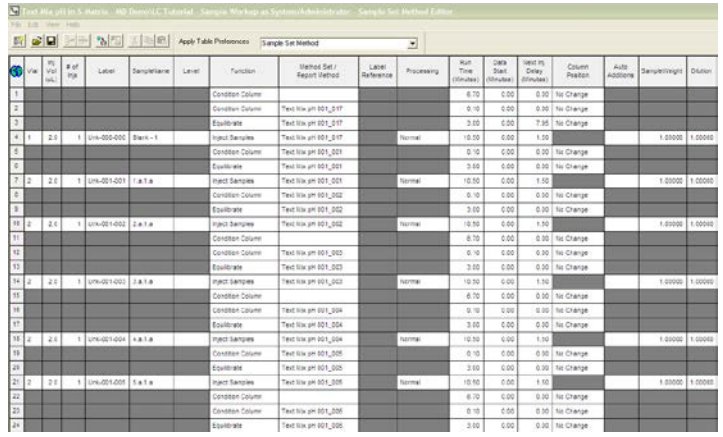
Automatically Retrieve All Chromatogram Results Da

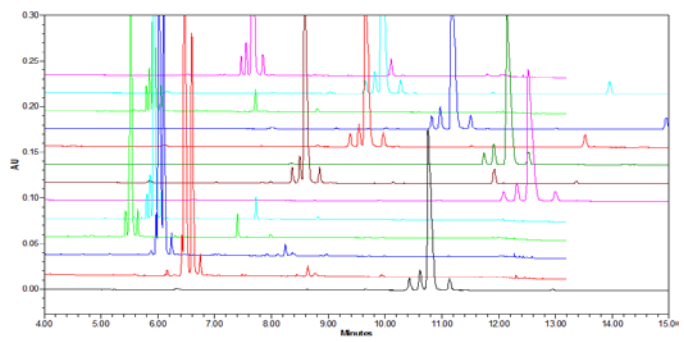
Automated analysis, graphing, and reporting.

Report formats:
RTF, DOC, HTML, PDF, XLSX, XML

Fusion QbD automatically imports all important test results from the CDS for all compounds.

Chromatography Data Software (CDS)





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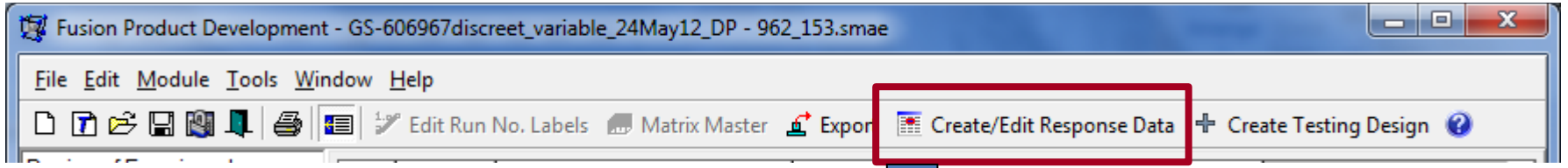
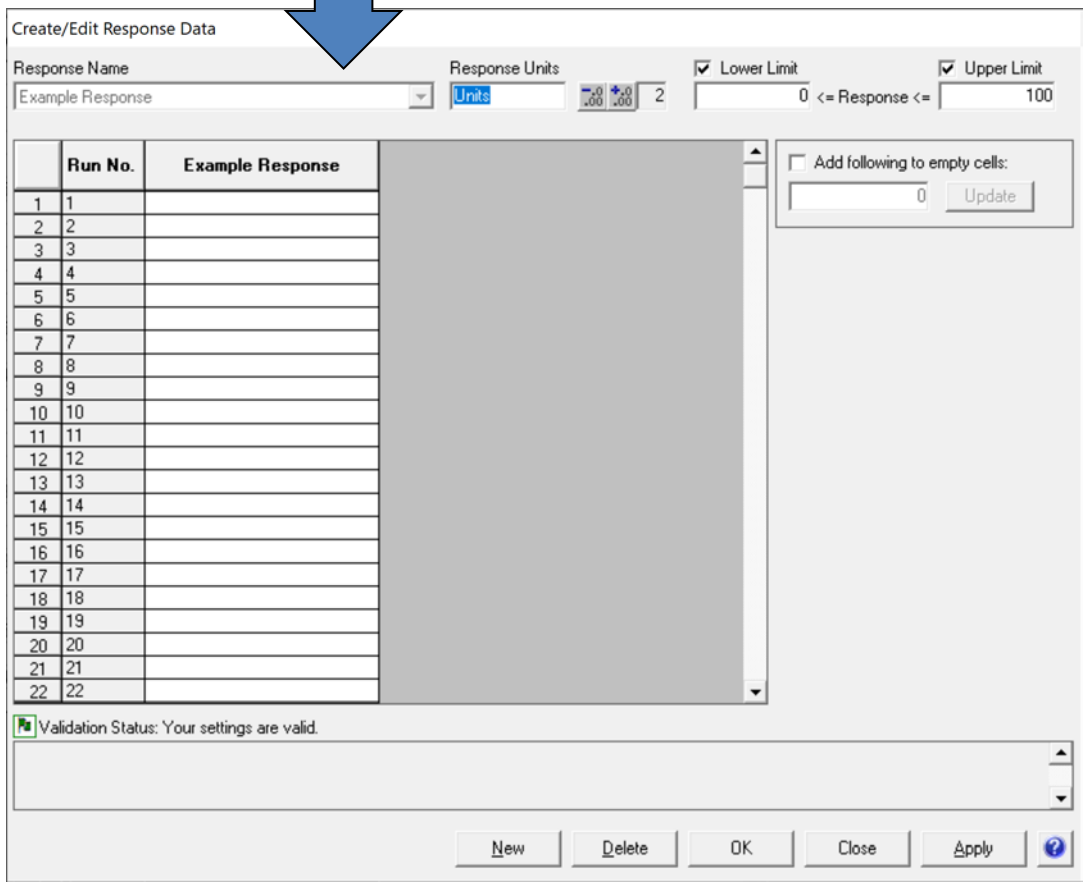
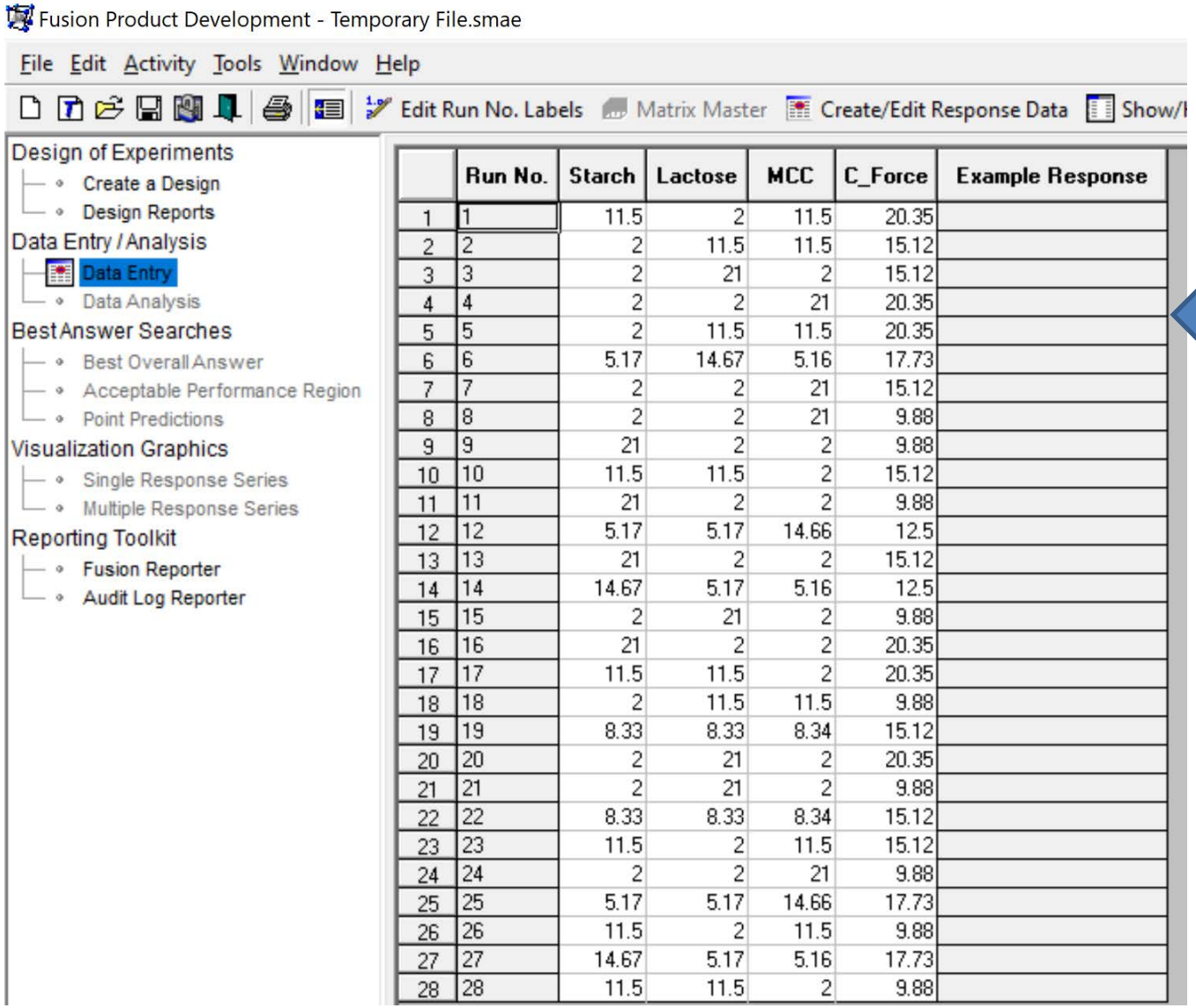
Simple Data Entry – One Test Result Per Trial



Responses consisting of only one measurement per run (no test repeats) can be entered directly.



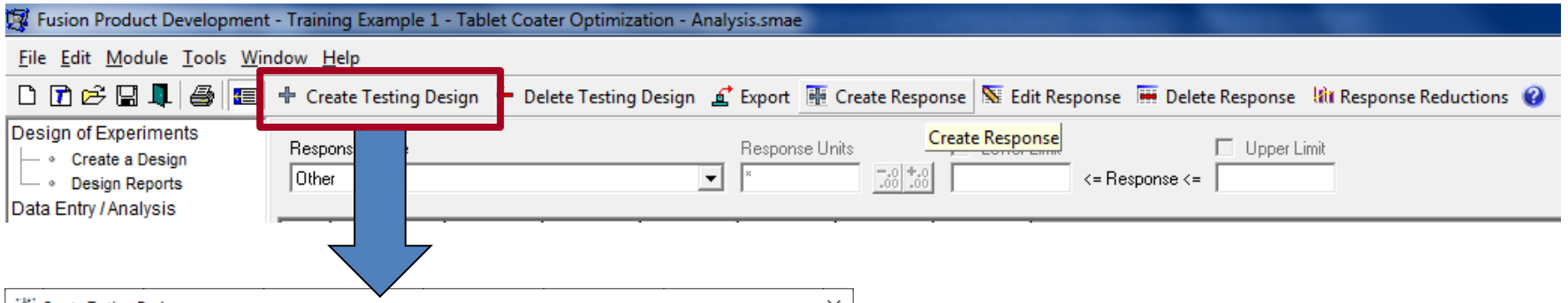
Simple Data Entry – One Test Result Per Run

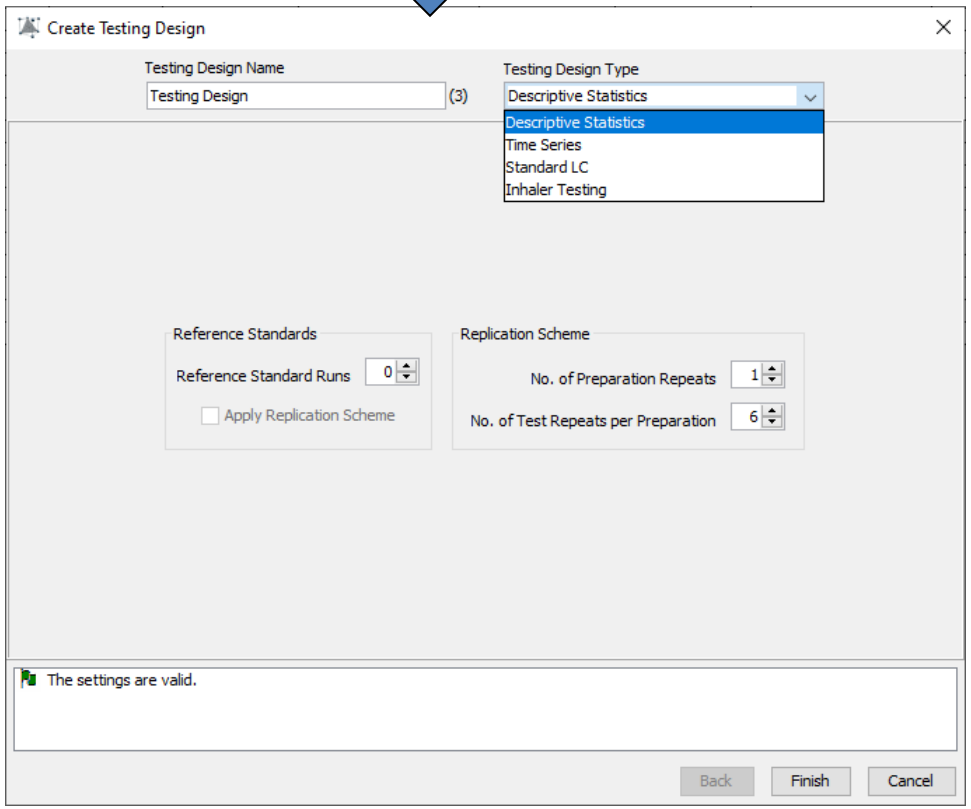


	Run No.	Starch	Lactose	MCC	C_Force	Example Response
1	1	11.5	2	11.5	20.35	
2	2	2	11.5	11.5	15.12	
3	3	2	21	2	15.12	
4	4	2	2	21	20.35	
5	5	2	11.5	11.5	20.35	
6	6	5.17	14.67	5.16	17.73	
7	7	2	2	21	15.12	
8	8	2	2	21	9.88	
9	9	21	2	2	9.88	
10	10	11.5	11.5	2	15.12	
11	11	21	2	2	9.88	
12	12	5.17	5.17	14.66	12.5	
13	13	21	2	2	15.12	
14	14	14.67	5.17	5.16	12.5	
15	15	2	21	2	9.88	
16	16	21	2	2	20.35	
17	17	11.5	11.5	2	20.35	
18	18	2	11.5	11.5	9.88	
19	19	8.33	8.33	8.34	15.12	
20	20	2	21	2	20.35	
21	21	2	21	2	9.88	
22	22	8.33	8.33	8.34	15.12	
23	23	11.5	2	11.5	15.12	
24	24	2	2	21	9.88	
25	25	5.17	5.17	14.66	17.73	
26	26	11.5	2	11.5	9.88	
27	27	14.67	5.17	5.16	17.73	
28	28	11.5	11.5	2	9.88	

Placeholder for Direct Data Entry

Response Data Handler™ Wizards





All Raw Test Results Data from All Platforms Entered, Managed, Converted to Modelable Data, and Audited in One Fusion QbD Experiment Workbook File.

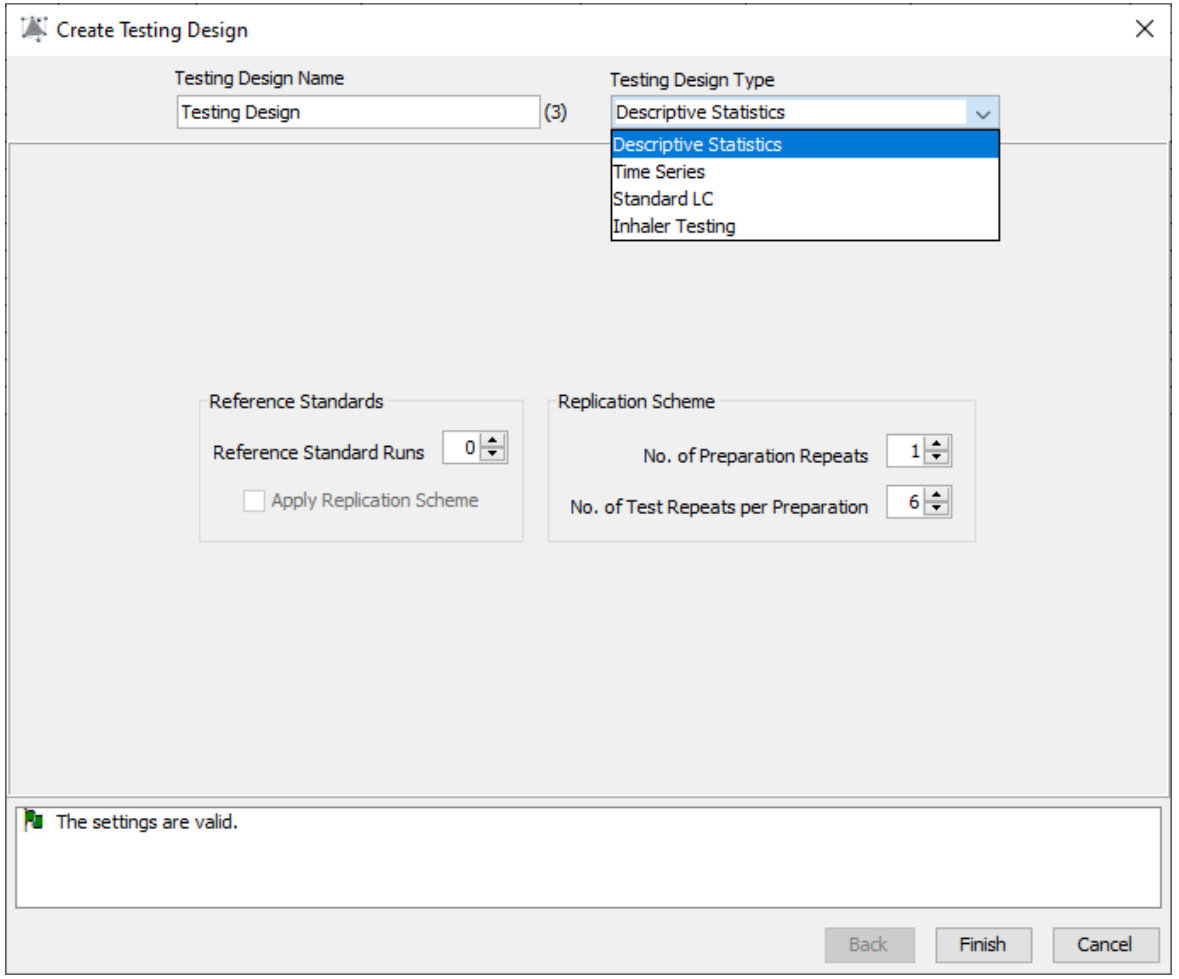
Response Data Handler™ Wizards

U.S. Patents No. 8,209,149 and 8,560,276

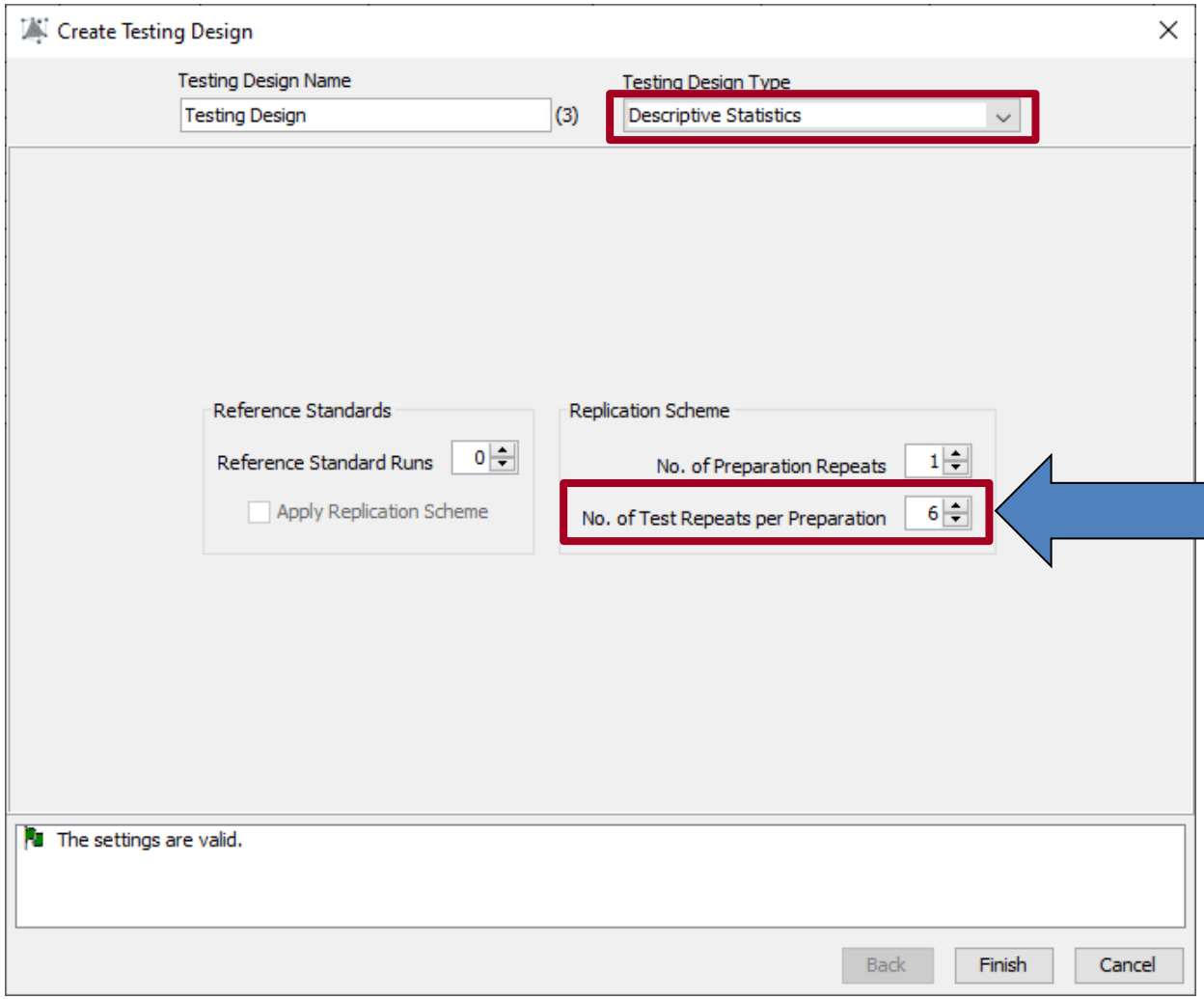
Handle Complex Data Simply and Easily!

Testing Design Setup Modes

- **Descriptive Statistics**
  Multiple test results per run.
- **Time Series**
  Testing at multiple time points per run.
- **Standard LC**
  Testing at multiple time points per run.
- **Inhaler Testing**
  Respiratory drug test results.



Descriptive Statistics Testing – Multiple Test Repeats per Run

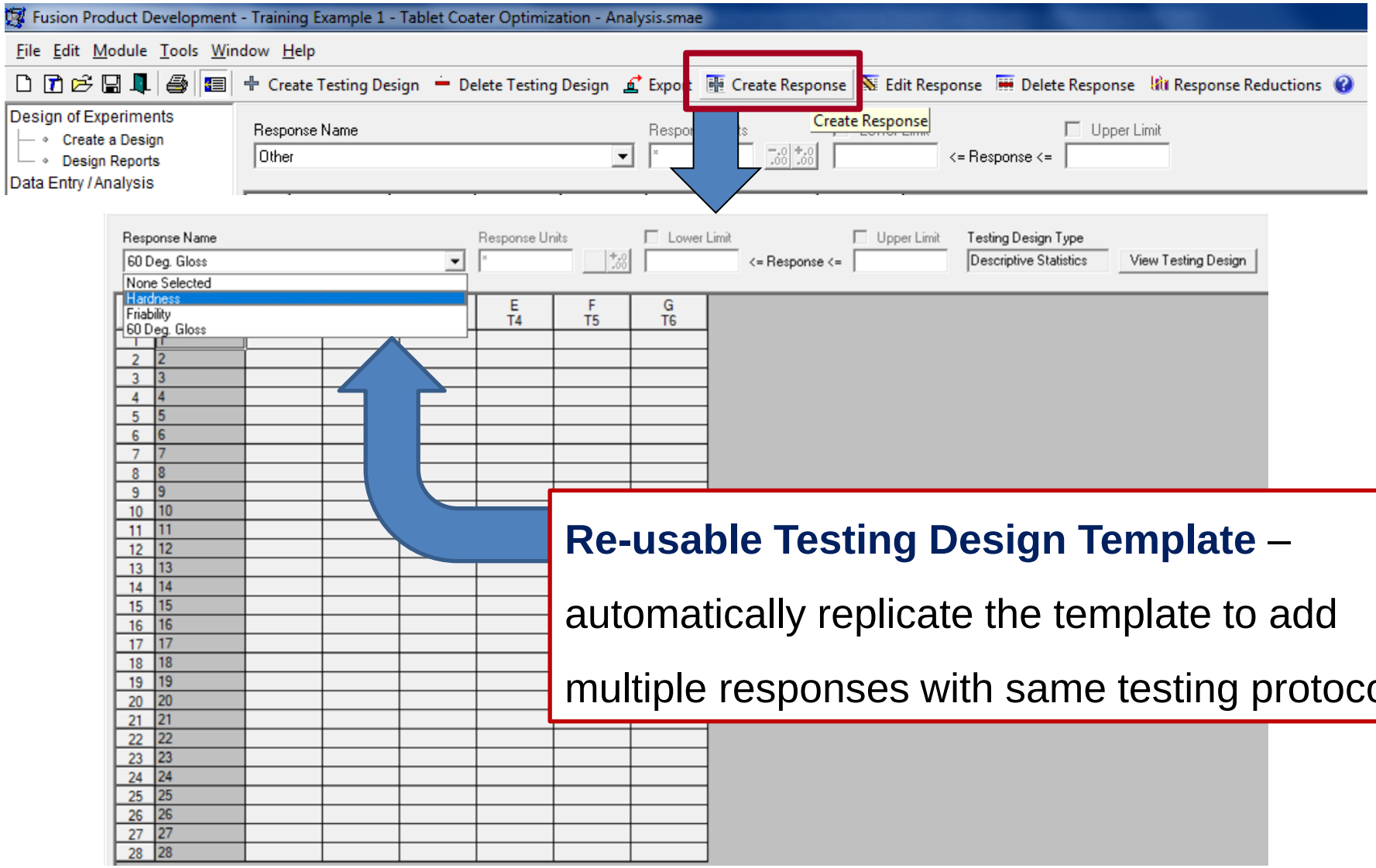


Example Protocol –

Test six (6) tablets for physical properties:

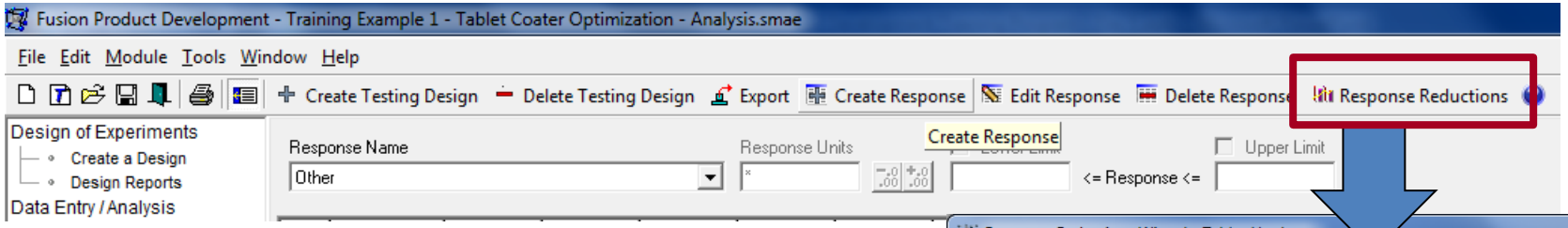
- Hardness
- Friability
- Gloss
- …

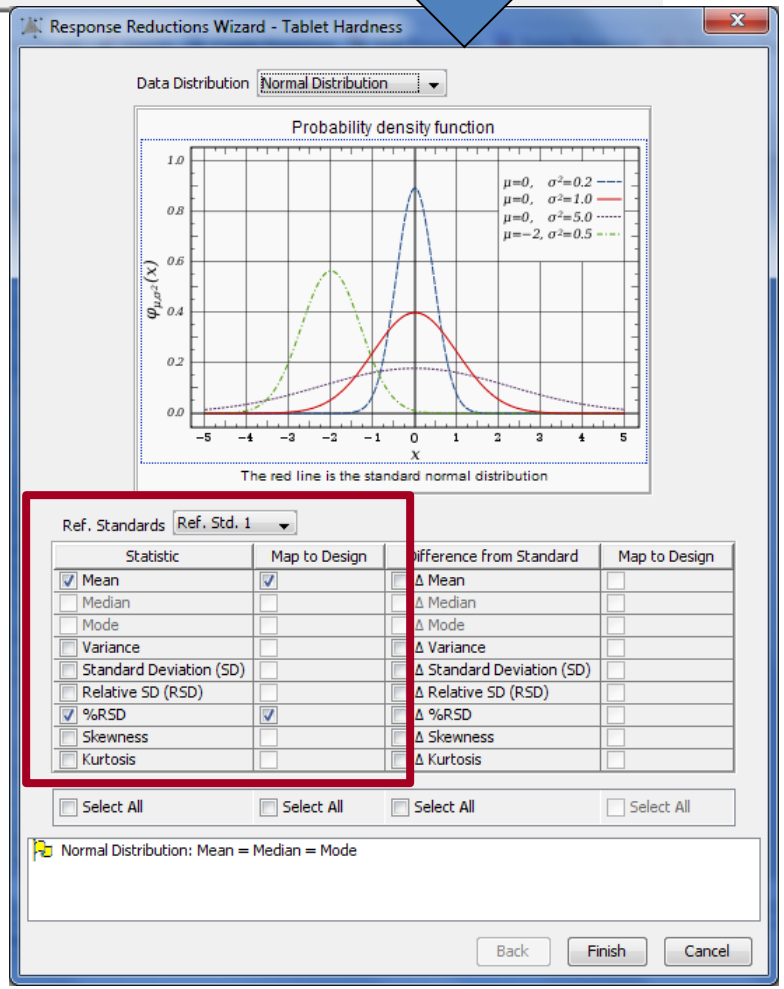
Descriptive Statistics – Testing Template



Re-usable Testing Design Template – automatically replicate the template to add multiple responses with same testing protocol.

Descriptive Statistics – Automated Response Generation

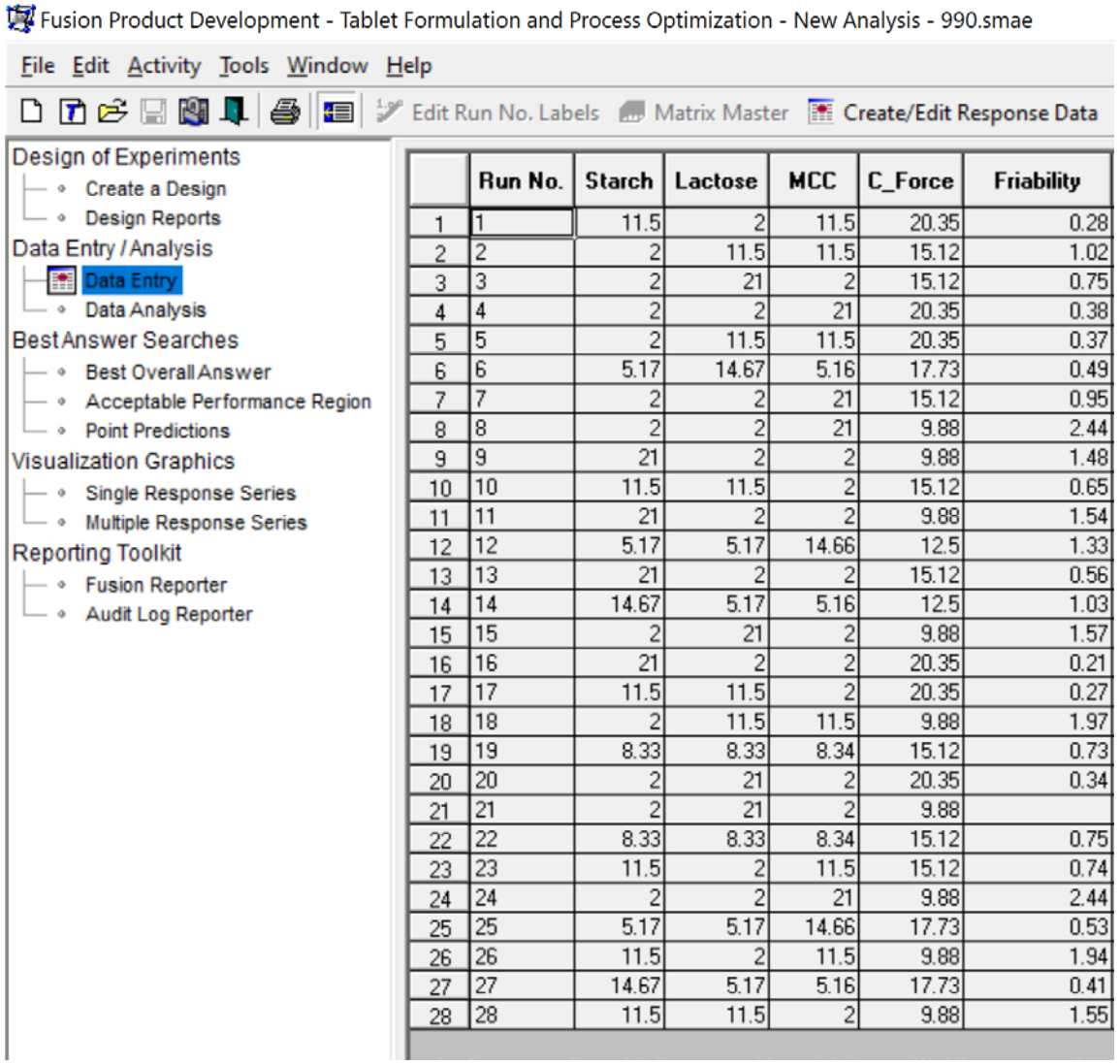




Automated Response Reductions:

- Handles test repeat data
- Handles non-normally distributed data
- Computes descriptive statistics responses
  E.g., Mean, Variance, Std. Dev., % RSD
- Computes differences of all statistics from a reference standard
- Maps all computed responses to the experimental design for analysis

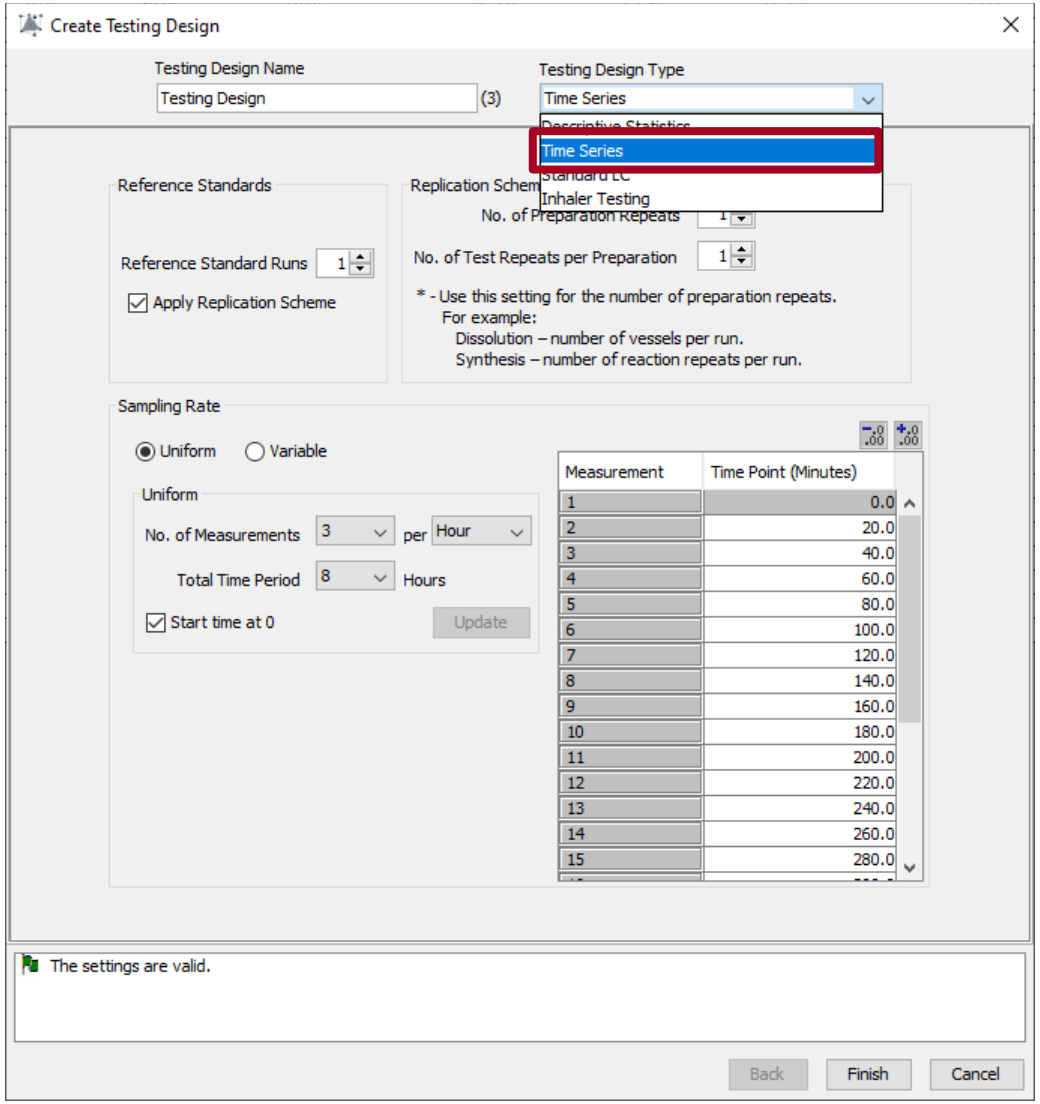
Descriptive Statistics – Automated Response Generation



	Run No.	Starch	Lactose	MCC	C_Force	Friability
1	1	11.5	2	11.5	20.35	0.28
2	2	2	11.5	11.5	15.12	1.02
3	3	2	21	2	15.12	0.75
4	4	2	2	21	20.35	0.38
5	5	2	11.5	11.5	20.35	0.37
6	6	5.17	14.67	5.16	17.73	0.49
7	7	2	2	21	15.12	0.95
8	8	2	2	21	9.88	2.44
9	9	21	2	2	9.88	1.48
10	10	11.5	11.5	2	15.12	0.65
11	11	21	2	2	9.88	1.54
12	12	5.17	5.17	14.66	12.5	1.33
13	13	21	2	2	15.12	0.56
14	14	14.67	5.17	5.16	12.5	1.03
15	15	2	21	2	9.88	1.57
16	16	21	2	2	20.35	0.21
17	17	11.5	11.5	2	20.35	0.27
18	18	2	11.5	11.5	9.88	1.97
19	19	8.33	8.33	8.34	15.12	0.73
20	20	2	21	2	20.35	0.34
21	21	2	21	2	9.88	
22	22	8.33	8.33	8.34	15.12	0.75
23	23	11.5	2	11.5	15.12	0.74
24	24	2	2	21	9.88	2.44
25	25	5.17	5.17	14.66	17.73	0.53
26	26	11.5	2	11.5	9.88	1.94
27	27	14.67	5.17	5.16	17.73	0.41
28	28	11.5	11.5	2	9.88	1.55

Automatically Computes your Selected Results and Transfers them to the Main Grid for Instant Analysis

Time Series – Multiple Time Point Tests per Run



E.g., Dissolution Testing

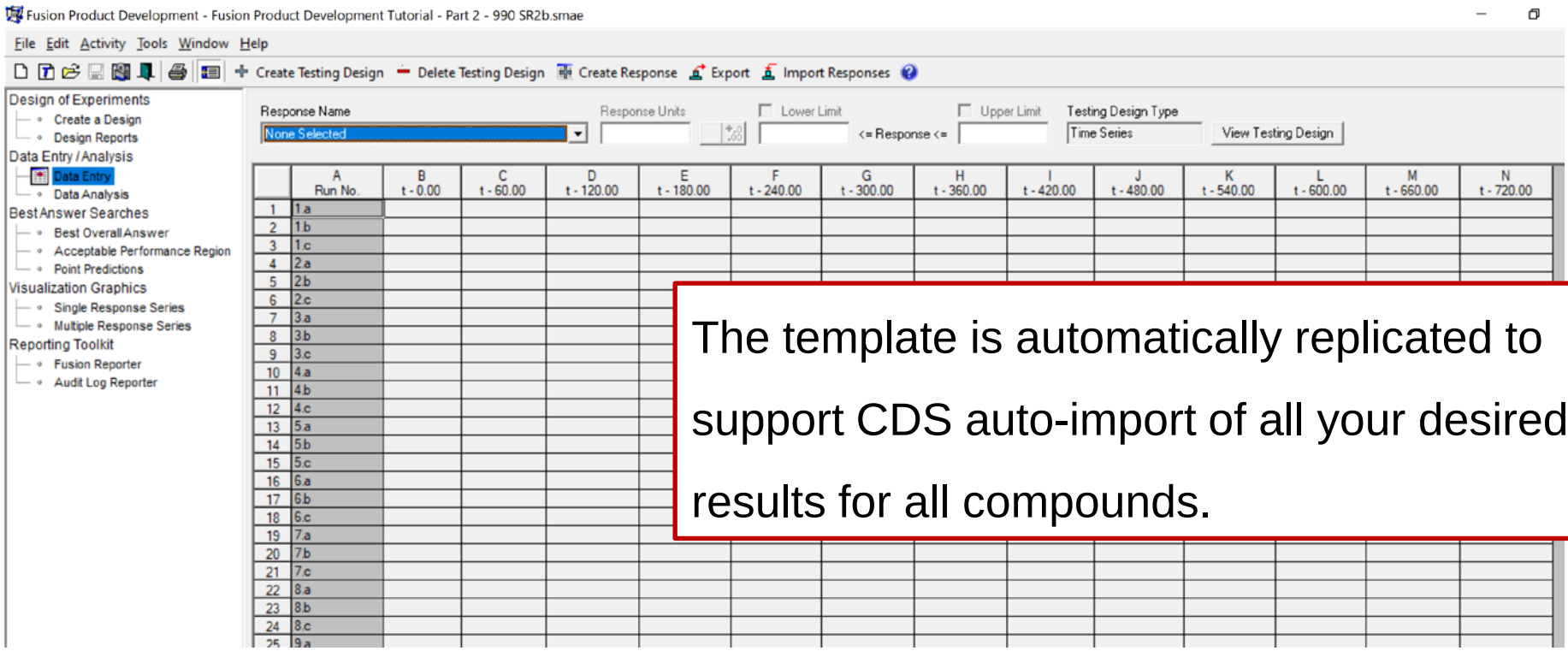
Time Series – Instant Testing Protocol

Supports:

- Uniform or variable time-point testing protocols
- Multiple sample preparation repeats
- Multiple test repeats at each time point
- Internal test standard data

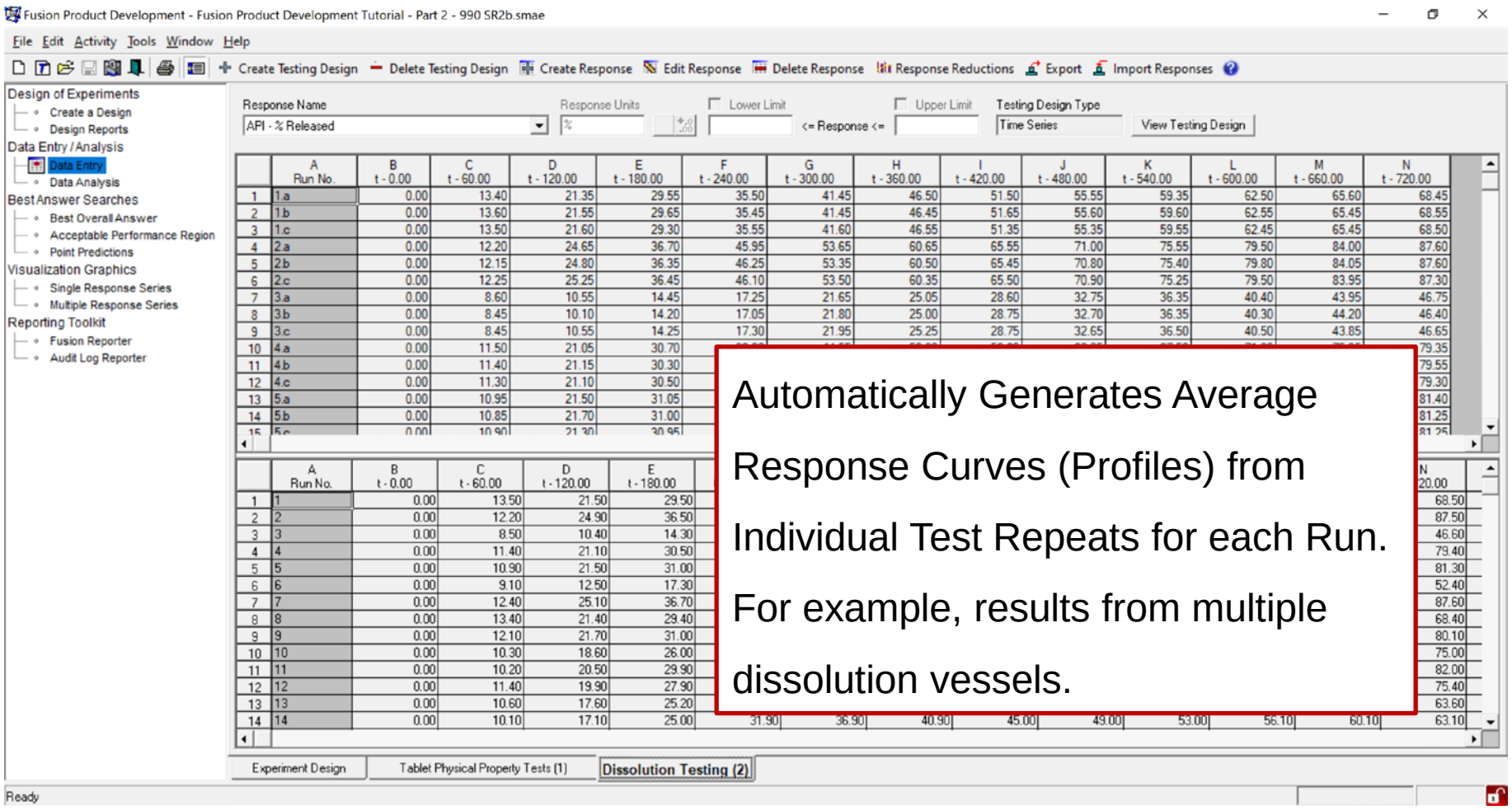
Time Series – Testing Template

Re-usable Testing Design Template



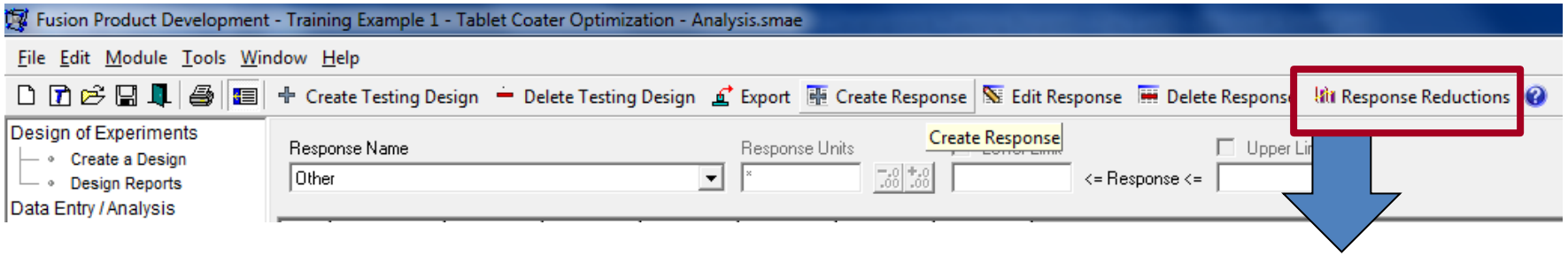
The template is automatically replicated to support CDS auto-import of all your desired results for all compounds.

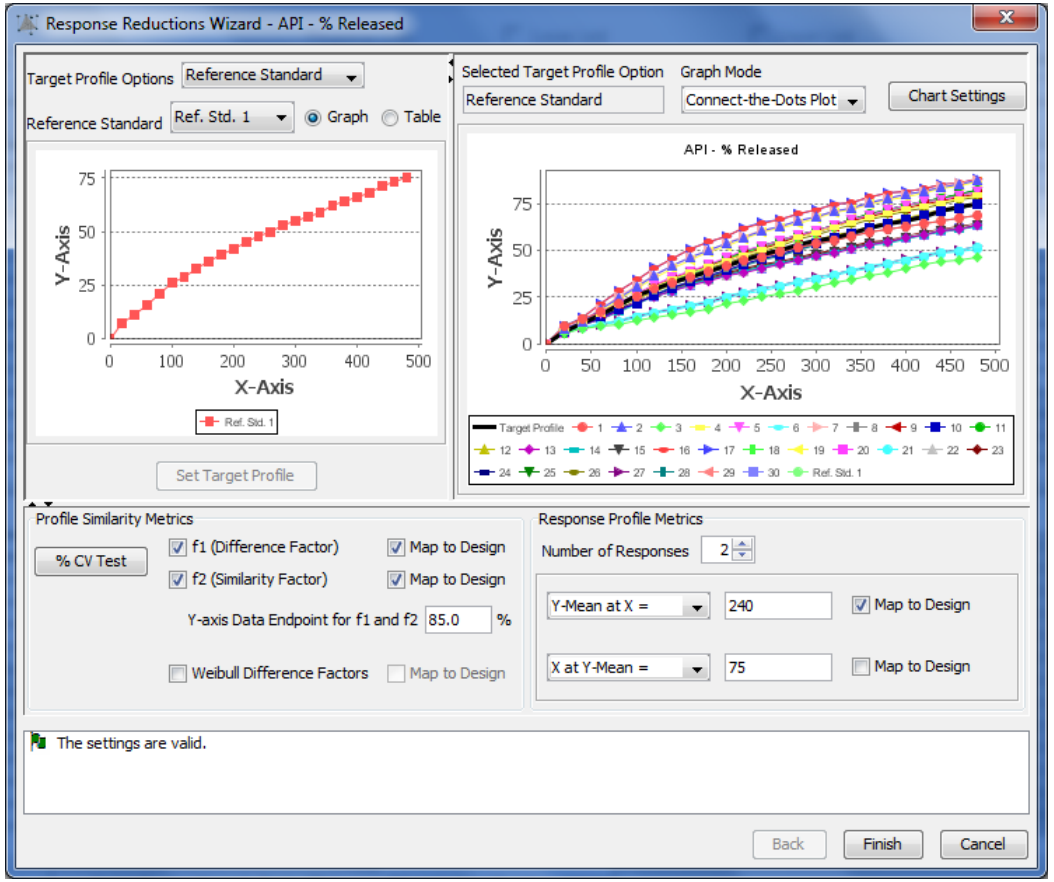
Time Series – Multiple Time Point Tests per Run



Automatically Generates Average Response Curves (Profiles) from Individual Test Repeats for each Run. For example, results from multiple dissolution vessels.

Time Series – Multiple Time Point Tests per Run



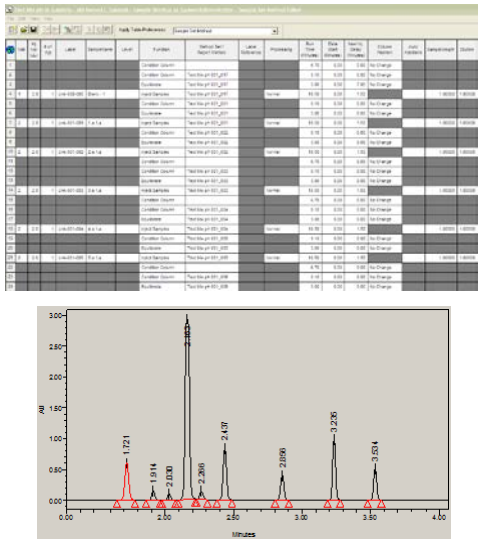


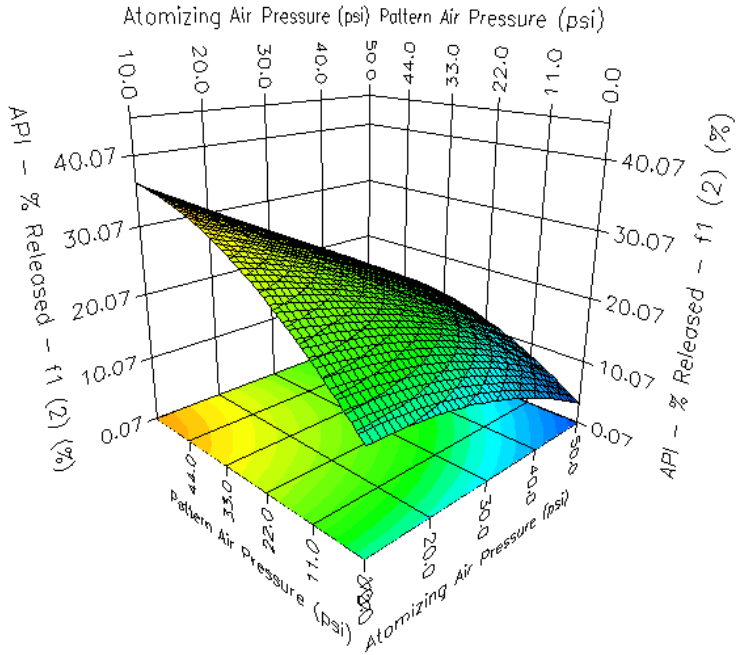
Coordinated Response Reductions:

- Handles test repeat data
- Computes average profiles
- Computes f1 & f2 curve fit metrics
- Computes sensitive Weibull curve fit metrics
- Computes additional profile response metrics

1-Click Modeling Turns Data into Knowledge

Multivariate DOE Study – goal is characterizing all significant effects of the study parameters on all Critical Quality Attributes (CQAs)





$$CQA = 9.3 + 4.2(AAP) - 5.4(PAP)^2 + 12.7(AAP*PFP) + 1.3(PAP*CP) + 1.6[(G.D.)^{2*}CP] + \ldots$$

Linear Effect | Curvature Effect | Interaction Effects | Complex Effect

Key Benefits of Fusion Process Development

- Supports All Install Environments (Citrix Ready Certified) ✓
- Full 21 CFR Part 11 Compliance Support ✓
- Flexible, Automated (1-Click) Design and Analysis ✓
- Full LC Testing Automation ✓
- Simplifies Handling of Complex Data ✓
- **Integrated Monte Carlo Robustness** ✓
- Full QbD Reporting ✓

QbD Robustness – Regulatory Statements 2012

Monte Carlo Robustness Simulation

"*Statistical treatments (e.g., **Monte Carlo simulations)** can help evaluate the effects of uncertainty.*"

Points to Consider for Design Space – A Regulatory Perspective, Elaine Morefield, Ph.D., 2012 Annual Meeting, AAPS.

Statistical Robustness Metrics

The FDA has stated that accepted process capability indexes such as **C_p, C_{pk}, C_{pm}, and C_{pkm}** are also part of the QbD toolset.

US FDA, Quality by Design: Objectives, Benefits, and Challenges, Lawrence X. Yu, Ph.D., 2012 Annual Meeting, AAPS.

QbD Robustness – Regulatory Statements 2018

3. Process Capability

Process capability refers to the performance of the process when it is operating under statistical control. Two capability indices are usually computed: C_p and C_{pk} in a similar way as was described with P_p and P_{pk}. However, C_p measures the **potential** capability in the process, if the process was centred, while C_{pk} measures the actual capability in a process which is off-centre or biased. If a process is centred, then $C_p = C_{pk}$.

$$C_{pk} = \min\left[\frac{U-\bar{X}}{3S_w}, \frac{\bar{X}-L}{3S_w}\right] \qquad (1.5)$$

The critical thing to note is that whilst the formulae for P_{pk} and C_{pk} look very similar, the standard deviation used to calculate the reference interval for C_{pk} is not S_t but S_w.

S_w is the within batch standard deviation (called the within sub group standard deviation in ISO) not the overall process standard deviation. It is usually estimated from a Shewhart mean and range control chart using the formula

Analytical Procedure Lifecycle Management

European Compliance Agency, Analytical Quality Control Group, July 2018, Final_r1

Fusion QbD – Integrated Monte Carlo Robustness

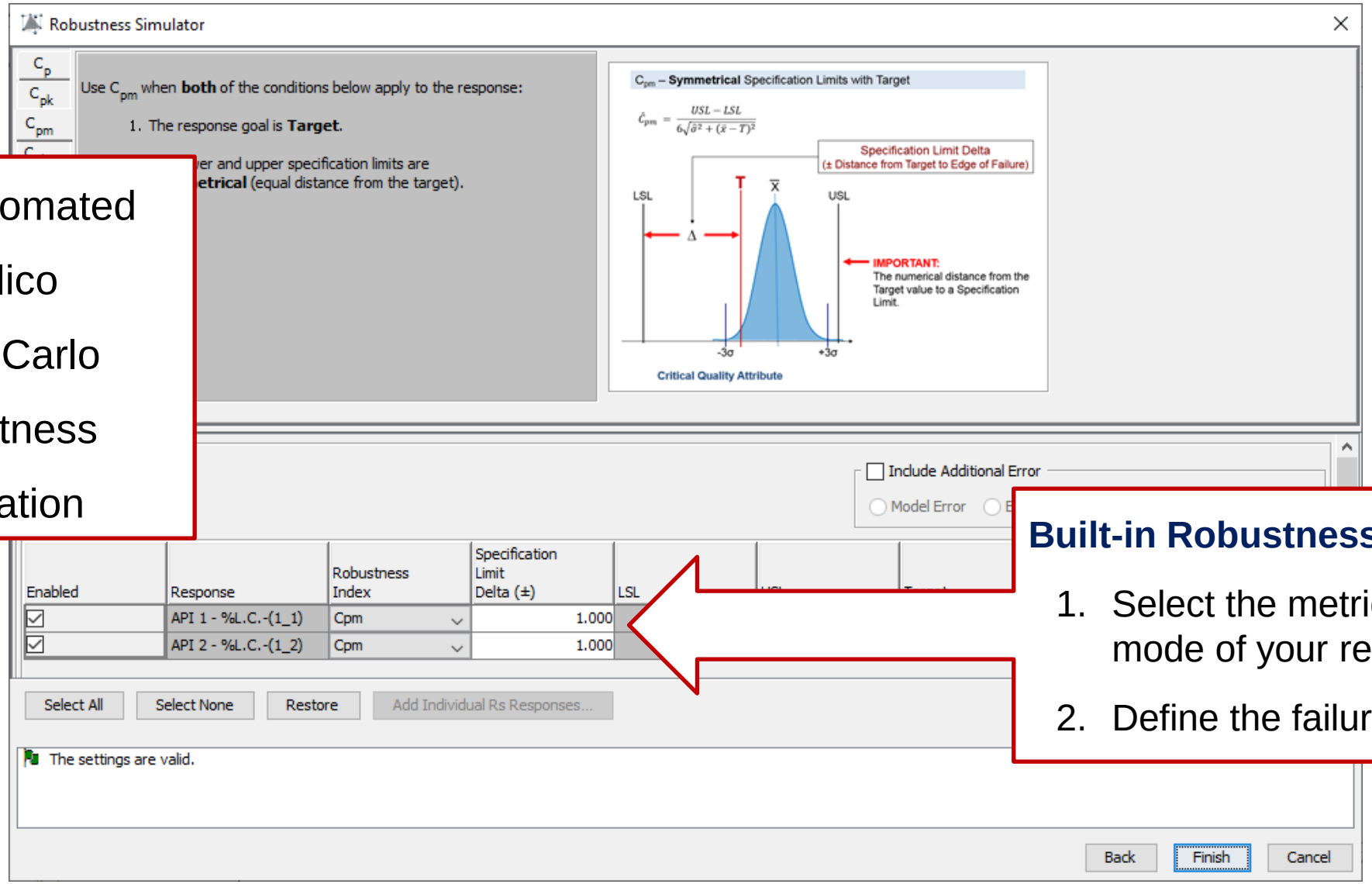
Fully Automated

In-silico

Monte Carlo

Robustness

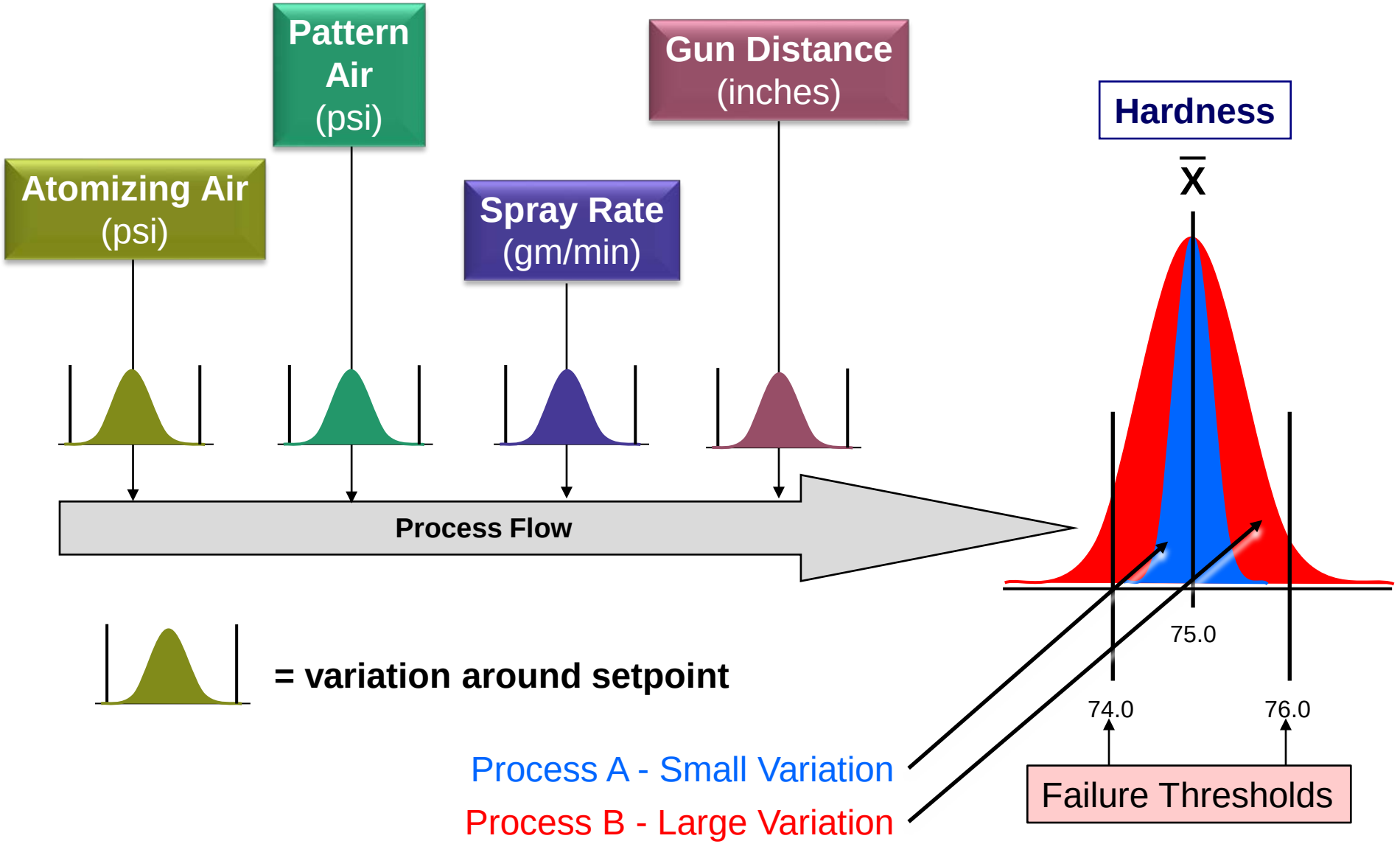
Simulation



Built-in Robustness Metrics – Simply:

1. Select the metric for the failure mode of your response (CQA).
2. Define the failure limit(s).

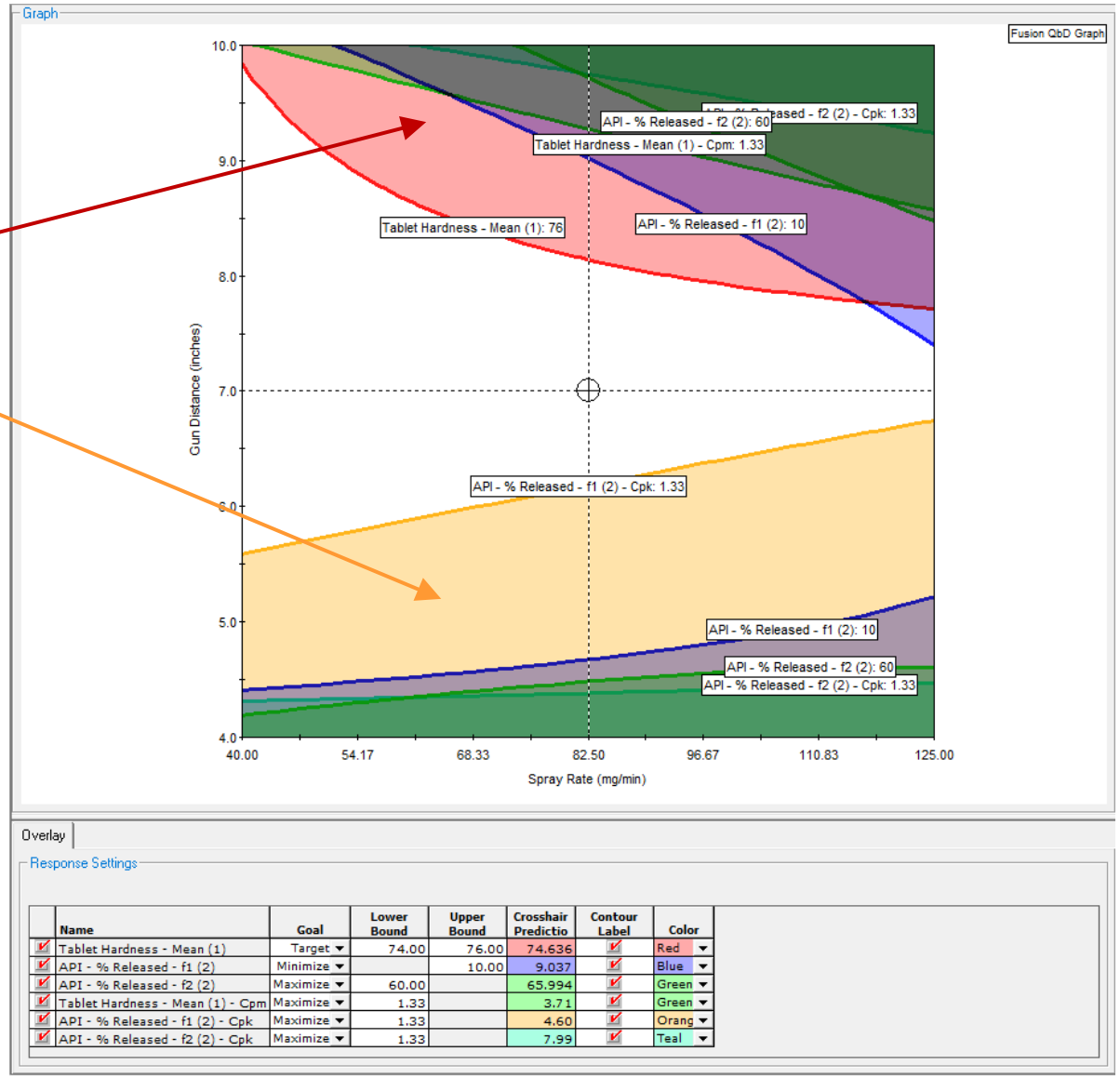
Robustness Simulation – Performance Variation in 10,000 Runs



Mean Performance and Integrated Robustness

Region of Failure – Mean Hardness

Region of Failure– % Rel. Robustness



	Name	Goal	Lower Bound	Upper Bound	Crosshair Predictio	Contour Label	Color
☑	Tablet Hardness - Mean (1)	Target	74.00	76.00	74.636	☑	Red
☑	API - % Released - f1 (2)	Minimize		10.00	9.037	☑	Blue
☑	API - % Released - f2 (2)	Maximize	60.00		65.994	☑	Green
☑	Tablet Hardness - Mean (1) - Cpm	Maximize	1.33		3.71	☑	Green
☑	API - % Released - f1 (2) - Cpk	Maximize	1.33		4.60	☑	Orang
☑	API - % Released - f2 (2) - Cpk	Maximize	1.33		7.99	☑	Teal

Key Benefits of Fusion Process Development

- Supports All Install Environments (Citrix Ready Certified) ✓
- Full 21 CFR Part 11 Compliance Support ✓
- Flexible, Automated (1-Click) Design ✓
- Full LC Testing Automation ✓
- Simplifies Handling of Complex Data ✓
- Integrated Monte Carlo Robustness ✓
- **Full QbD Reporting** ✓

Reporting Harmonized with Regulatory Guidances

ICH Q8(R2) – Page 22

C. Presentations of Design Space

Example 1: Response graphs for dissolution are depicted as a surface plot (Figure 1a) and a contour plot (Figure 1b). Parameters 1 and 2 are factors of a granulation operation that affect the dissolution rate of a tablet (e.g., excipient attribute, water amount, granule size.)

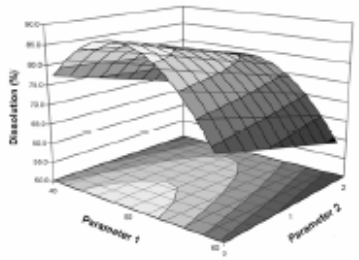


Figure 1a: Response surface plot of dissolution as a function of two parameters of a granulation operation. Dissolution above 80% is desired.

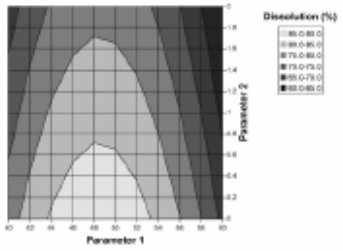


Figure 1b: Contour plot of dissolution from example 1a.

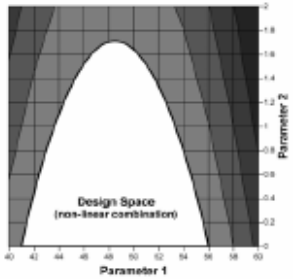


Figure 1c: Design space for granulation parameters, defined by a nonlinear combination of their ranges, that delivers satisfactory dissolution (i.e., >80%).

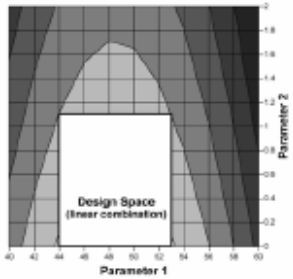


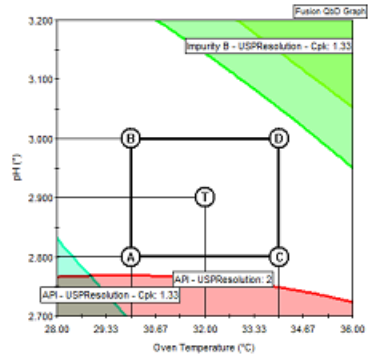
Figure 1d: Design space for granulation parameters, defined by a linear combination of their ranges, that delivers satisfactory dissolution (i.e., >80%).

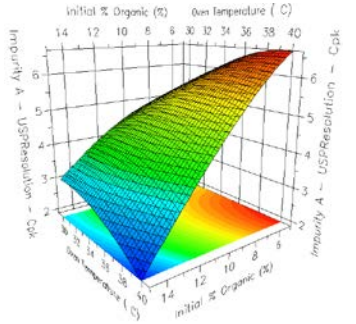
Fusion QbD

Name: Administrator
Company: S-Matrix
Project: Project 1
Date: October 29, 2015 6:31:03 PM PDT [GMT-07:00]

S-Matrix

D.S. + PARs - 10% Organic





Proven Acceptable Range Settings

Axis	Name	Units	Lower Bound	Upper Bound	Centerpoint
X	Oven Temperature	°C	30.00	34.00	32.00
Y	pH	-	2.800	3.000	2.900

Response Variable Goals

Name	Units	Goal	Lower Bound	Upper Bound	Color	Predicted Centerpoint
API - USPResolution	(*)	Maximize	2.00	---	Red	2.45
Impurity A - USPResolution	(*)	Maximize	2.00	---	Blue	3.59
Impurity B - USPResolution	(*)	Maximize	2.00	---	Green	2.39
API - USPTailing	(*)	Target	0.90	1.10	Orange	1.01
API - USPResolution - Cpk	(*)	Maximize	1.33	---	Teal	3.06
Impurity A - USPResolution - Cpk	(*)	Maximize	1.33	---	Purple	6.41
Impurity B - USPResolution - Cpk	(*)	Maximize	1.33	---	Lime	4.09
API - USPTailing - Cpm	(*)	Maximize	1.33	---	Sky	5.40

Graph Variable Settings

Name	Units	Graph Setting	Range/Level(s)
Oven Temperature	(°C)	X Axis Variable	28.00 <= Oven Temperature <= 36.00
pH	(*)	Y Axis Variable	2.700 <= pH <= 3.200
Initial % Organic	(%)	Constant	8.7

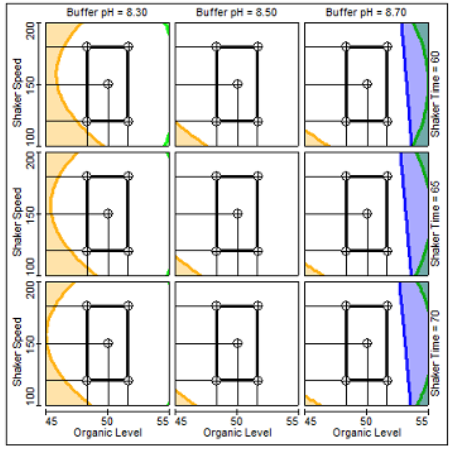
1 of 2

Reporting Harmonized with Regulatory Guidances

Name: Administrator
Company: S-Matrix
Project: API Assay Method (User Defined)
Date: 21 JUL 2020 07:35:03 PDT [UTC-07:00]

S-Matrix®

Robust Design Space Trellis



Response Variable Goals

Name	Units	Goal	Color	Lower Bound	Upper Bound
API 1 - %L.C.-(1_1)	*	Target	Red	97.50	99.50
API 2 - %L.C.-(1_2)	*	Target	Blue	98.70	100.70
API 1 - %L.C.-(1 1) - Cpm		Maximize	Orange	1.33	
API 2 - %L.C.-(1_2) - Cpm		Maximize	Green	1.33	

Proven Acceptable Range Settings

Axis	Name	Units	Lower Bound	Upper Bound	Centerpoint
X	Organic Level	%	48	52	50
Y	Shaker Speed	rpm	120	180	150

1 of 2

Trellis Variable Settings

Series	Variable Name	Units	Low	Middle	High
Horizontal	Buffer pH	*	8.30	8.50	8.70
Vertical	Shaker Time	min	60	65	70

Graph Variable Goals

Name	Units	Graph Setting	Range/Level(s)
Organic Level	%	X Axis Variable	45 <= Organic Level <= 55
Sonication Time	min	Constant	0
Shaker Speed	rpm	Y Axis Variable	100 <= Shaker Speed <= 200
Buffer pH	*	Horizontal Trellis Levels	8.30, 8.50, 8.70
Shaker Time	min	Vertical Trellis Levels	60, 65, 70

Experiment Variables for Robustness Simulator

Included	Variable Name	Units	Maximum Expected Variation (+/- 3 Sigma Value)
Yes	Buffer pH	*	0.20
Yes	Organic Level	%	2
No	Sonication Time	min	
Yes	Shaker Speed	rpm	5
Yes	Shaker Time	min	2

Responses for Robustness Simulator

Response Name	Robustness Index	Specification Limit (+/- distance from target)	LSL	USL	Target	Additional Error	Additional Error Amount (+/- 3 Sigma Value)
API 1 - %L.C.-(1_1)	Cpm	1.00	---	---	98.50	None	None
API 2 - %L.C.-(1 2)	Cpm	1.00	---	---	99.70	None	None

Report Settings

Setting	Value
Report Name	Robust Design Space Trellis
Action	Report Created
Report Type	Trellis Graph
Graph Category	Process
Include PARs	Checked
Include Verification Runs	Unchecked
Include Verification Runs in Report	Unchecked

2 of 2

Reports can be output in a variety of file formats:

PDF / MS Word / HTML / TXT / XLSX

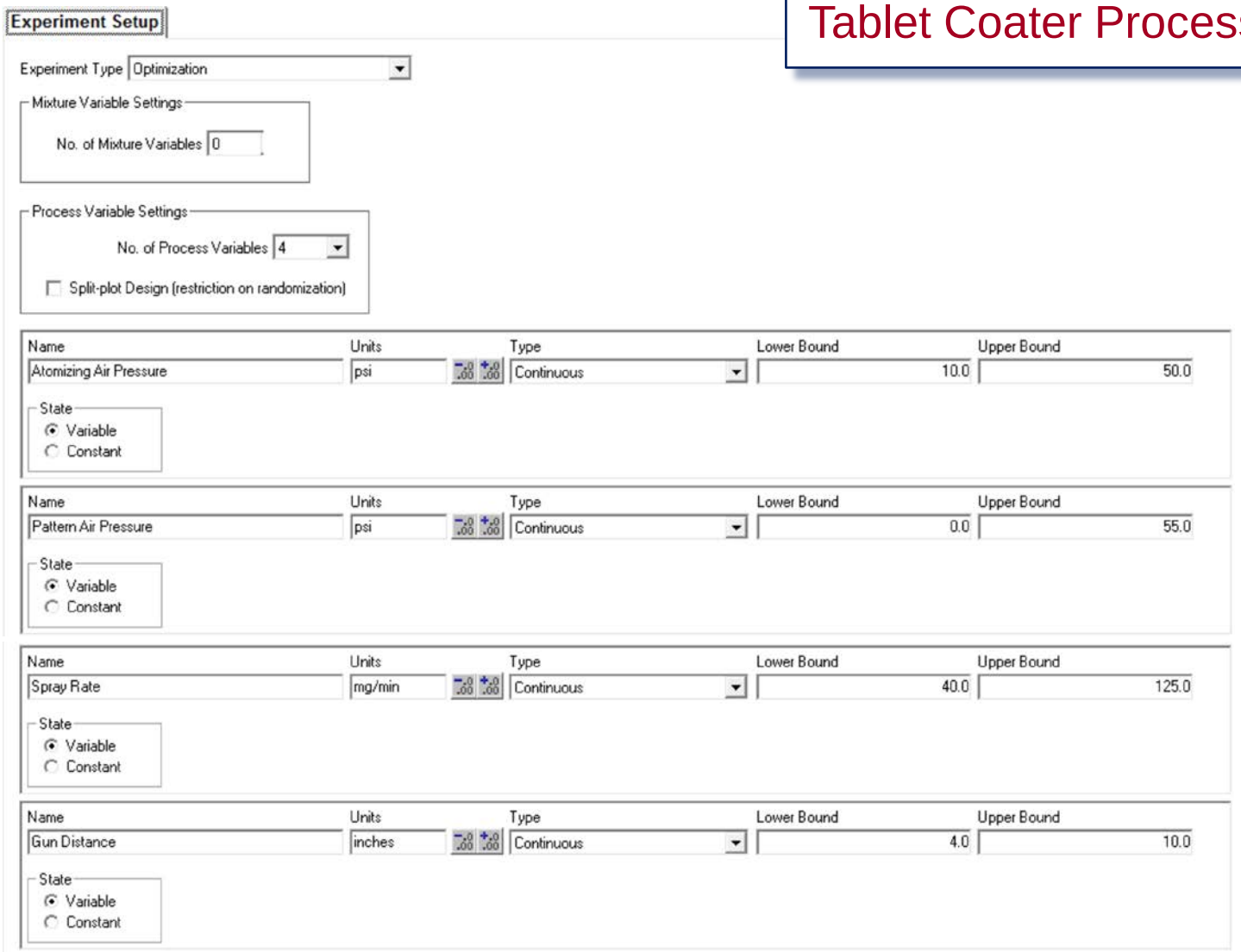
Example Applications

Tablet Coating Optimization

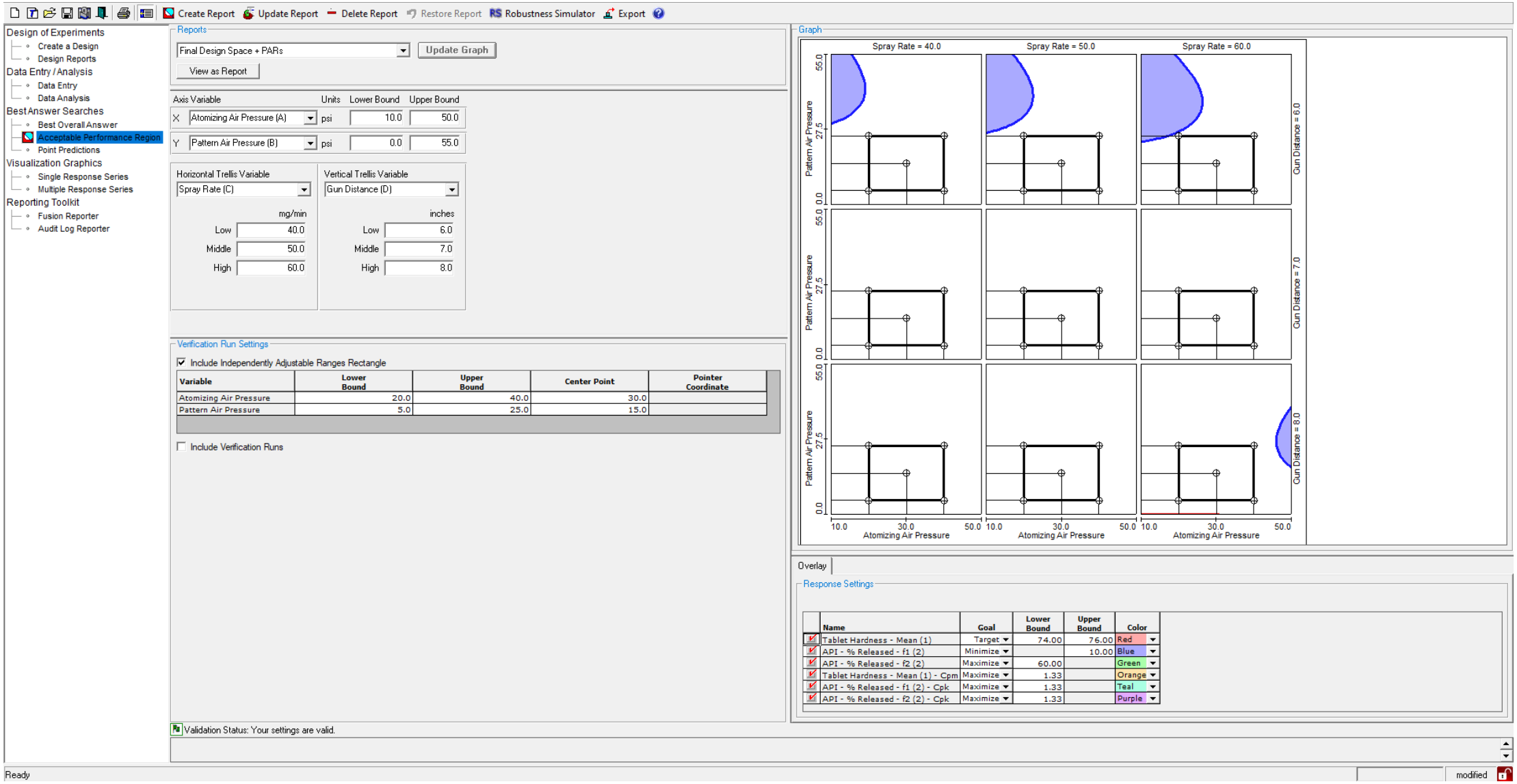
Tablet Excipient Formulation and Process Optimization

Example 1 – Tablet Coater Optimization

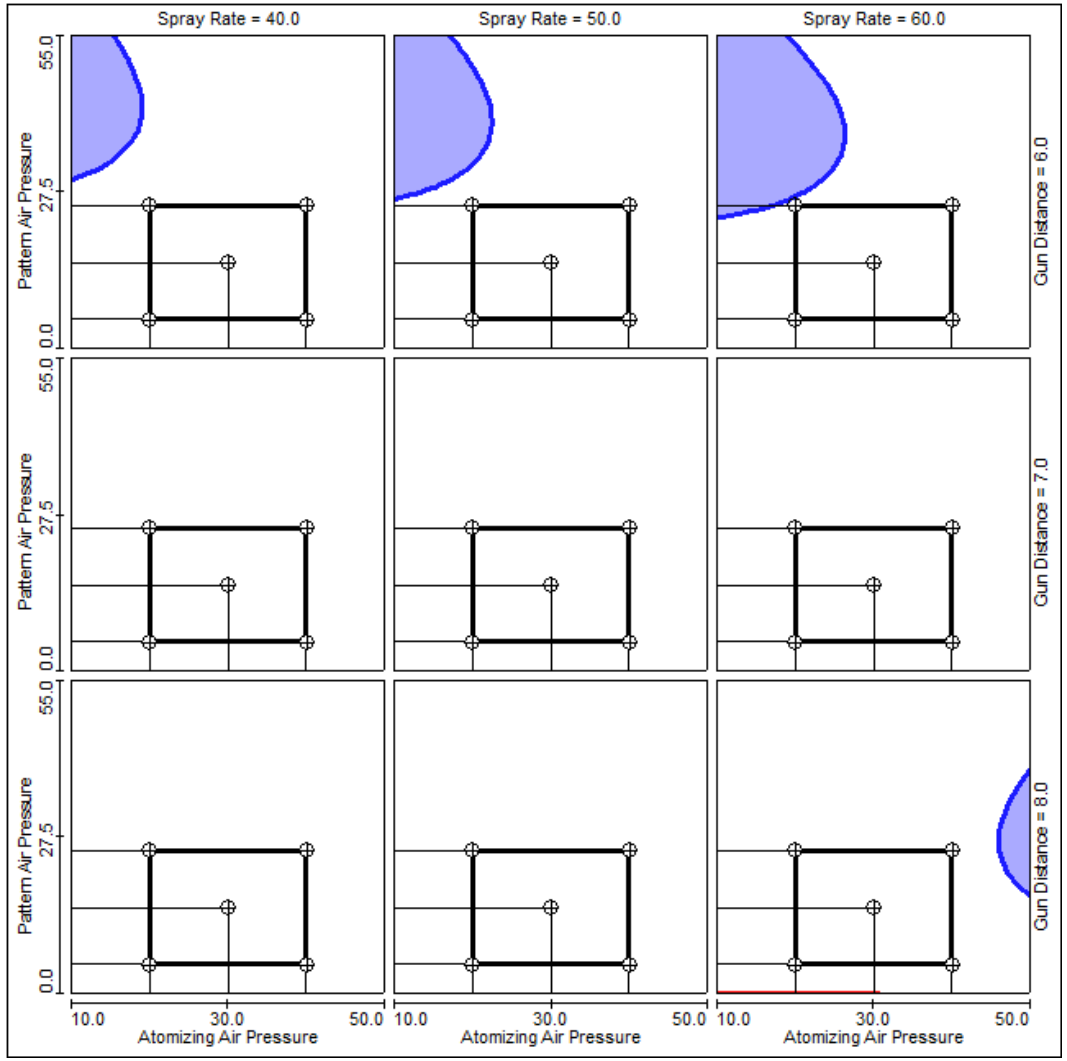
Tablet Coater Processes Optimization Study



4-Factor Trellis – Mean Performance and Robustness



4-Factor Trellis – Mean Performance and Robustness



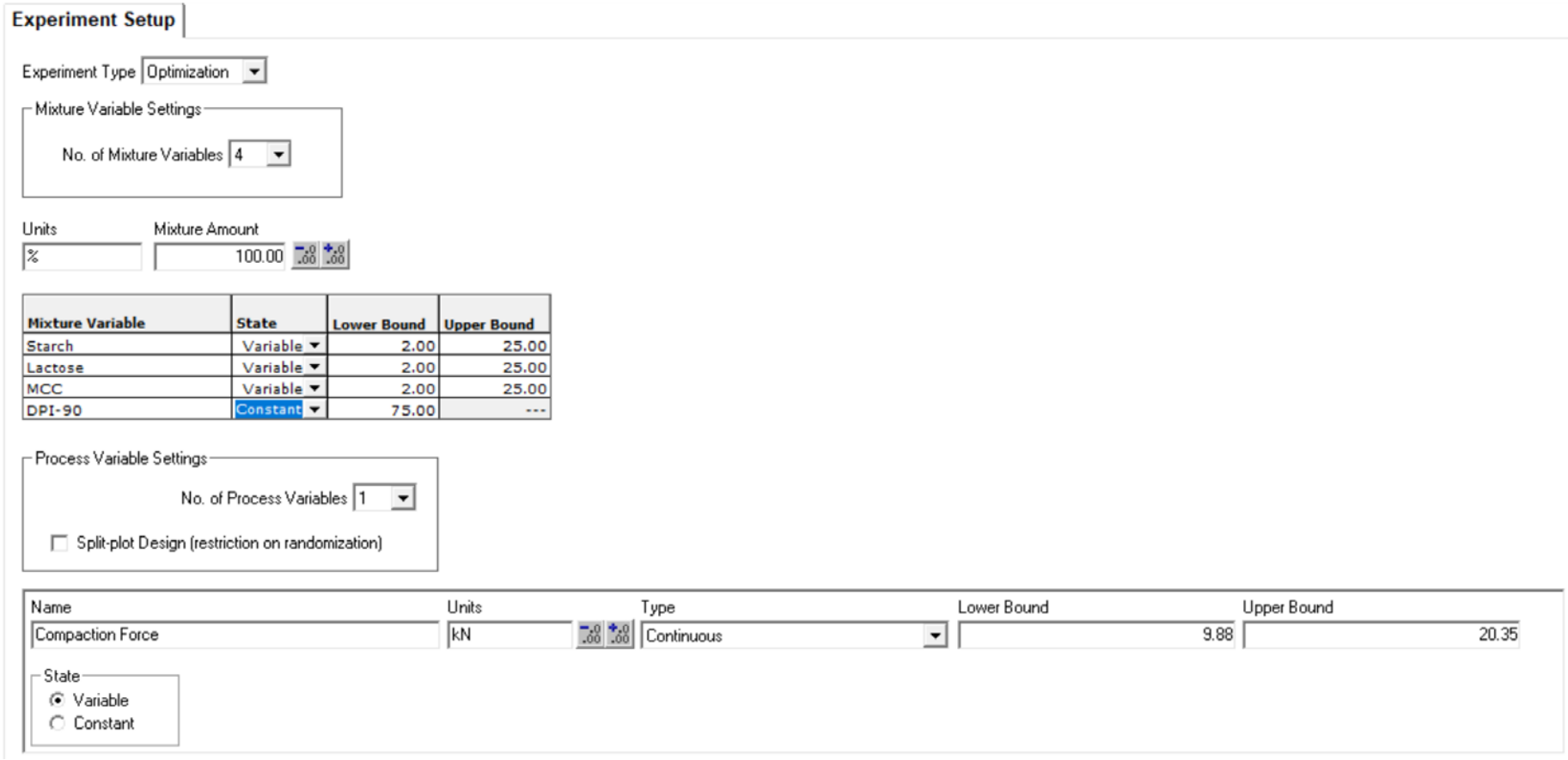
Independently Adjustable Ranges

Variable	Lower Bound	Upper Bound	Center Point
Atomizing Air Pressure	20.0	40.0	30.0
Pattern Air Pressure	5.0	25.0	15.0

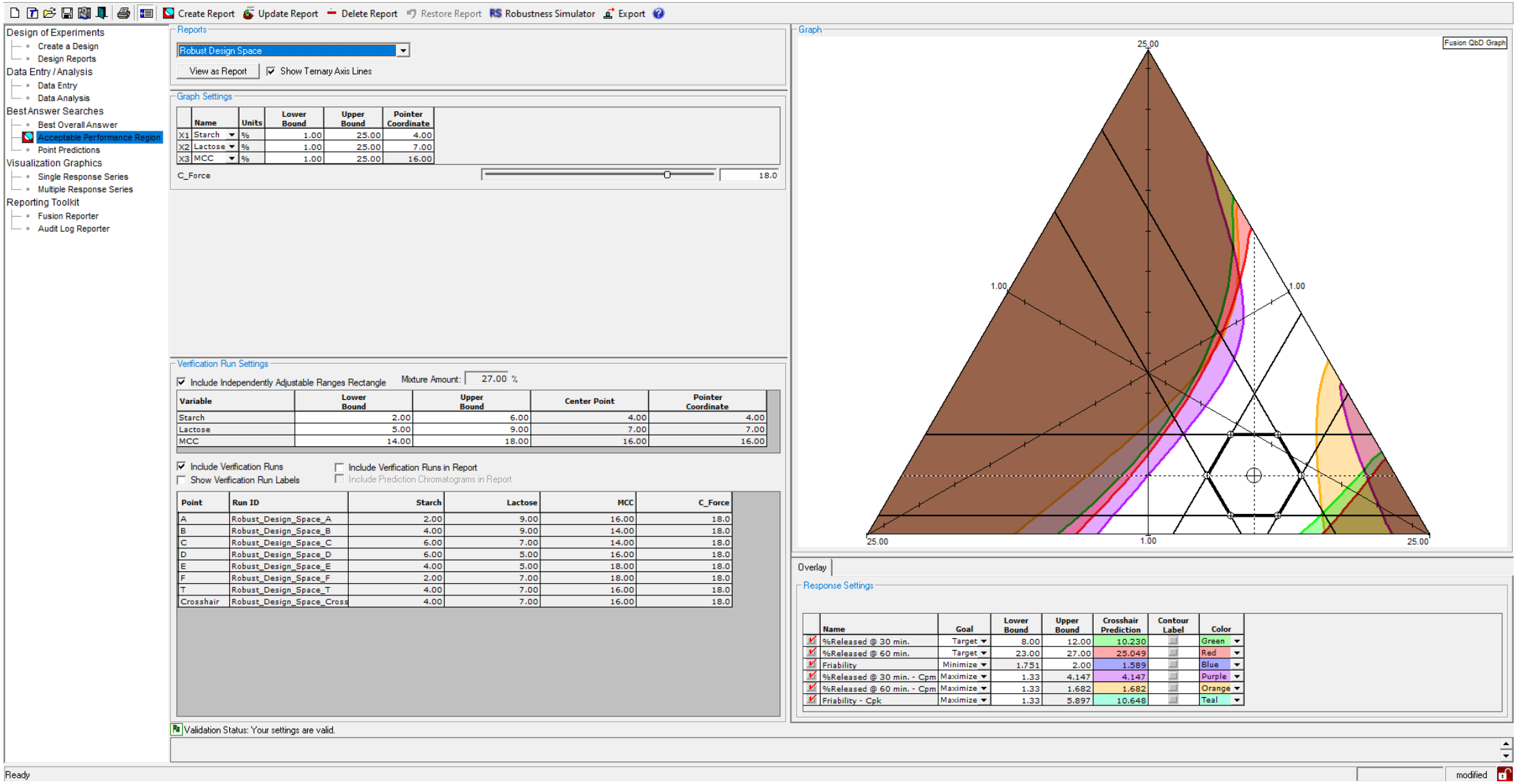
Spray Rate	40	60	50
Gun Distance	6	8	7

Example 2 – Tablet Excipient Formulation and Critical Process Factor Optimization

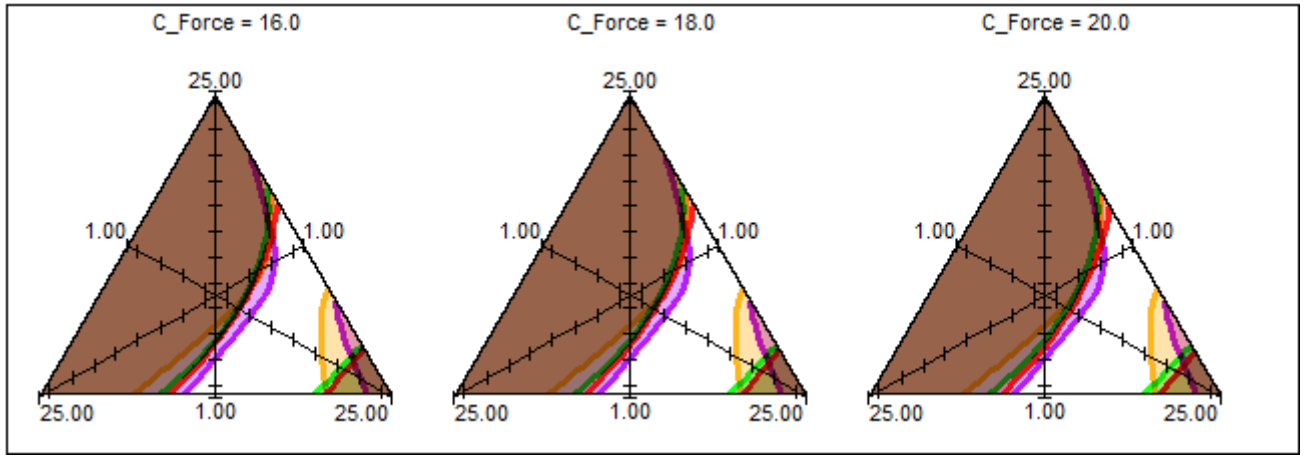
Formulation + Processes Optimization Study



Final Design Space – Mean Performance and Robustness



4-Factor Trellis – Mean Performance and Robustness



Independently Adjustable Ranges

Variable	Lower Bound	Upper Bound	Center Point
Starch	2.00	6.00	4.00
Lactose	5.00	9.00	7.00
MCC	14.00	18.00	16.00

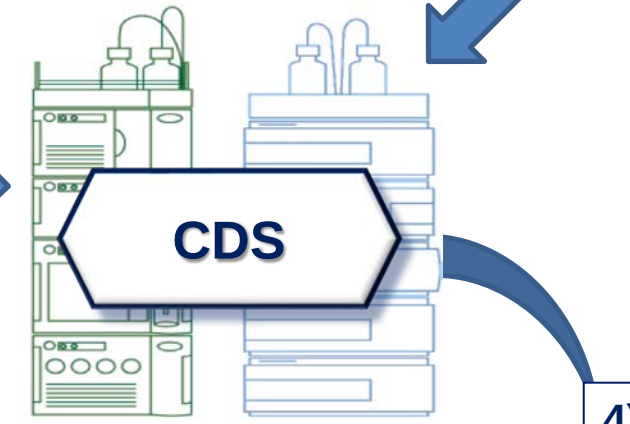
Compaction Force	16	20	18

Example Workflows

- **Sample Preparation Method Development**
- **Dissolution Method Development**
- **Respiratory Drug Development**

FPD – Sample Preparation Method Development

Sample Prep Expt. Workflow



1) Experiment Design

Fusion QbD generates the Sample Prep. Study based on the user's variable settings.

2) Testing Design

- Standard LC

3) Standard LC Testing

Resolution
Tailing
Plates
Area % RSD
S/N Ratio
Etc.

4) Results Data Import

Fusion QbD automatically imports all LC results for all compounds and maps the data to the Sample Prep. Study design for automated modeling.

FPD – Dissolution Method Development

Disso. Method Development Expt. Workflow

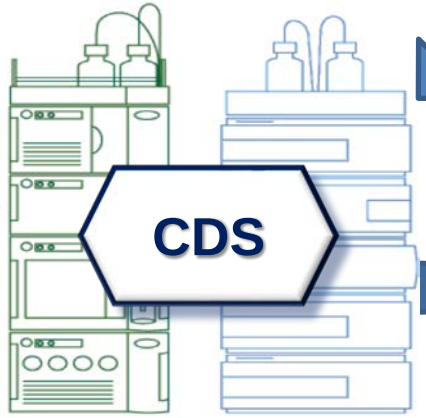
3) Time Series Testing

Dissolution

(% Rel. vs Time)

2) Testing Design

- Time Series



1) Experiment Design – e.g.

- Process – e.g.
  - o Time, Temp, Speed, …
- Chemistry – e.g.
  - o Buffer ΔC, pH, …

4) Results Data Import

All LC Results for all Compounds

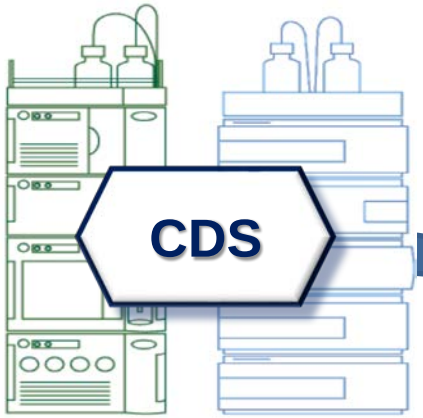
FPD – Respiratory Drug R&D

Respiratory Drug R&D Expt. Workflow

3) Impactor Testing

2) Testing Design

- Respiratory



1) Experiment Design

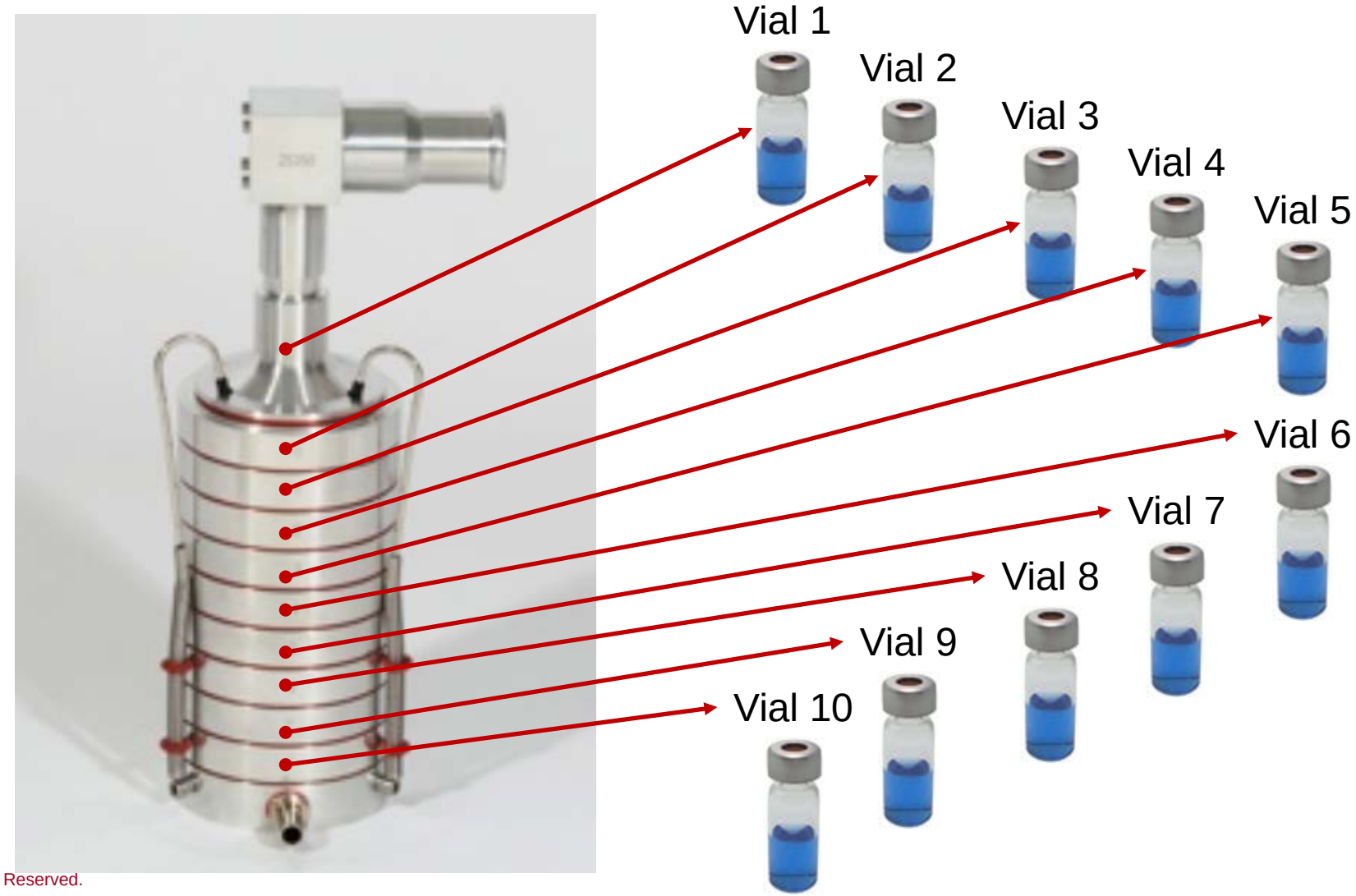
- Drug Formulation
- Delivery Device
  - Type / Config
- ...

4) Results Data Import

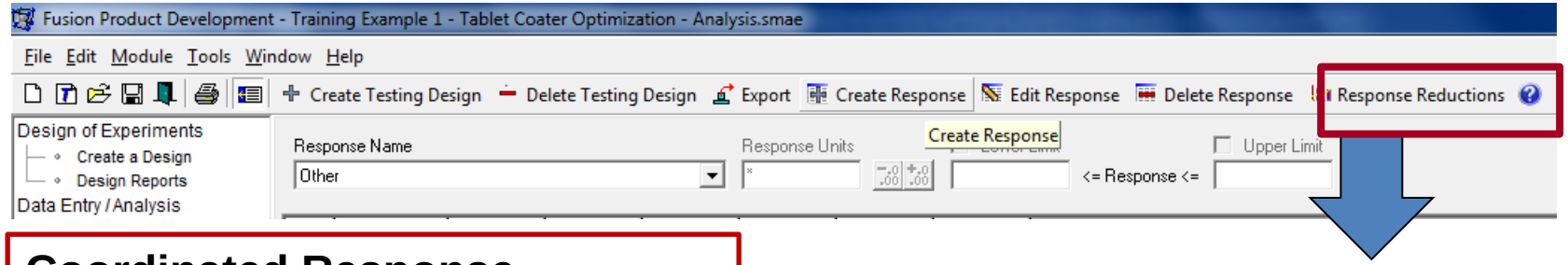
All LC Results for all Compounds

FPD – Respiratory Drug R&D

LC Testing Demand for Each Experiment Run

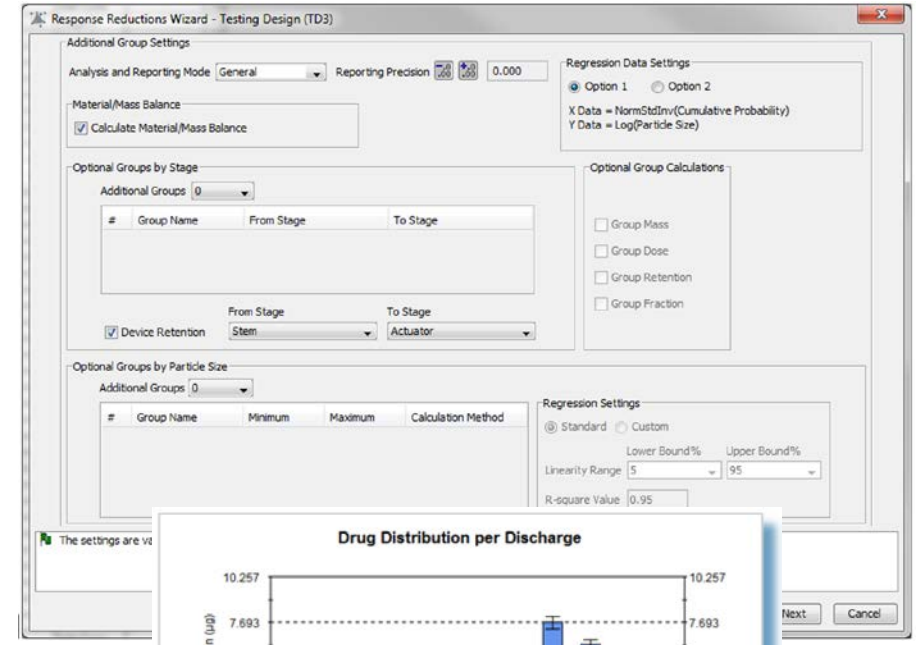


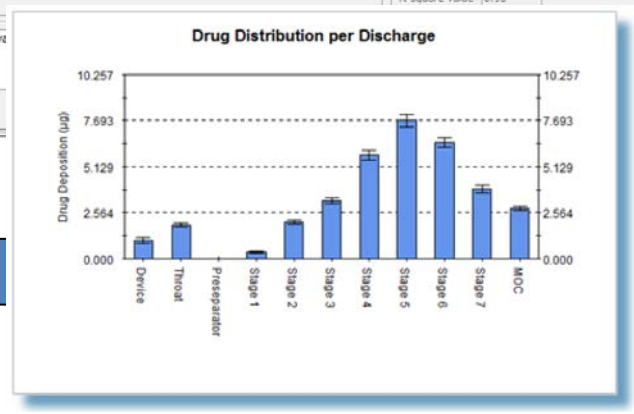
FPD – Respiratory Drug R&D



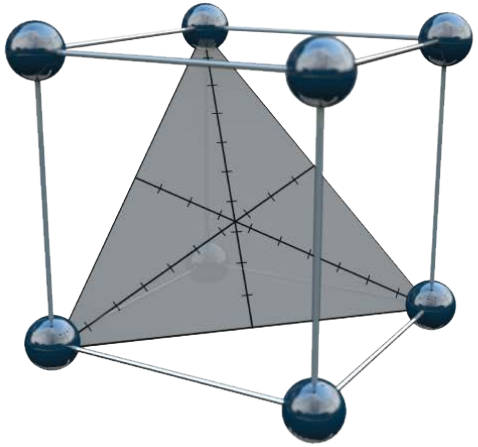
Coordinated Response Reductions:

- Mass Median Aerodynamic Diameter (MMAD)
- Geometric Standard Deviation (GSD)
- Fine Particle Dose (FPD)
- Fine Particle Fraction (FPF)
- Total Dose and Emitted Dose
- Interpolation and Regression Calc Options
- Data Grouping Options
- …





End of Presentation



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