Fusion Pro® – QbD-aligned DOE Software

- Statistical Experimental Design
- Analysis & Modeling
- Robustness Simulation
- Numerical & Graphical Optimization
- 2D, 3D, & 4D Visualization Graphics
- 100% aligned with Quality by Design Principles and Guidelines

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

Initial DOE Software Development and Verification

Software development began in the mid-1990s in consultation with recognized leaders in the field of Statistical Design of Experiments methodology.

DOE Verification by Douglas C. Montgomery, Ph.D.

Dr. Montgomery is a well known authority in the field of Industrial Statistics with a special emphasis on Design of Experiments. He is the author of the best selling book *Design and Analysis of Experiments* (John Wiley and Sons, Inc.). Dr. Montgomery has consulted in the development and verification of all major DOE features, including:

- Wizard guided experiment design selection
- Wizard guided data analysis
- Automated regression modeling capabilities

Initial DOE Software Development and Verification

DOE Verification by John A. Cornell, Ph.D.

Dr. Cornell is considered the foremost authority on mixture experiment design. He is the author of the best selling book *Experiments With Mixtures* (John Wiley and Sons, Inc.). Dr. Cornell worked closely with S-Matrix on development of our mixture design and analysis capabilities. Among the specific capabilities that he has guided and verified are:

- Unconstrained and Singly-constrained Mixture Designs
- Unconstrained and Singly-constrained Mixture-Process Designs
- Mixture-Process Designs with Multicomponent Constraints
- Analysis of Mixture and Mixture-Process Experiment Data

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Quality by Design (QbD)

"A systematic approach to development that begins with predefined objectives and **emphasizes product and process understanding** and process control, based on sound science and quality risk management.."

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."

QbD 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."

QbD Design Space

QbD 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."

Curves defining the acceptable performing regions are generated by equations (models)

IMPORTANT – interactions also induce curvature in response surfaces

The design space is the un-shaded overlapping region of acceptable performance

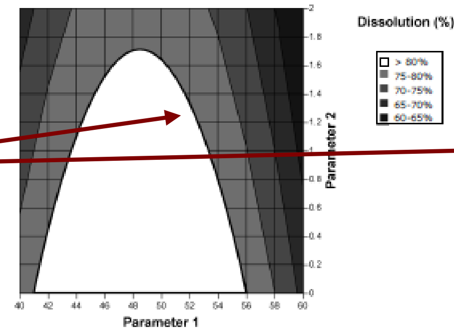


Figure 2a: Contour plot of dissolution as a function of Parameters 1 and 2.

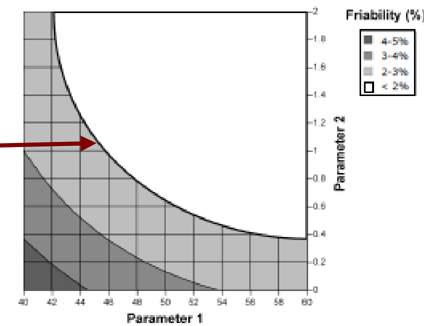


Figure 2b: Contour plot of friability as a function of Parameters 1 and 2.

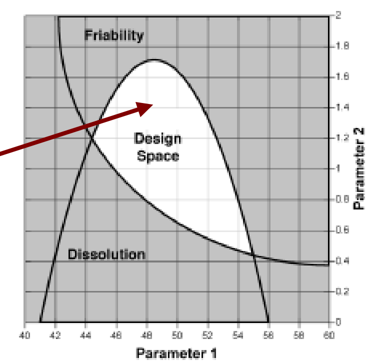


Figure 2c: Proposed design space, comprised of the overlap region of ranges for friability and or dissolution.

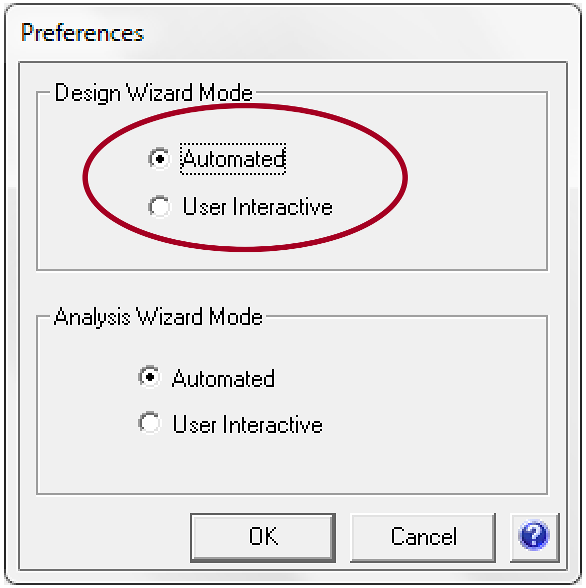
Fusion Pro – Critically Differentiating Features Which Support QbD-aligned R&D

1. **Automated Design of Experiments (DOE)**
2. **Response Data Handler**
3. **Automated Analysis and Modeling**
4. **Fully Integrated Monte Carlo Robustness Simulation**
5. **Best Answer Search Wizard**
6. **Design and Operating Space Characterization**

Feature 1 – Automated DOE

Integrated DOE with Automated and User-interactive Design Modes

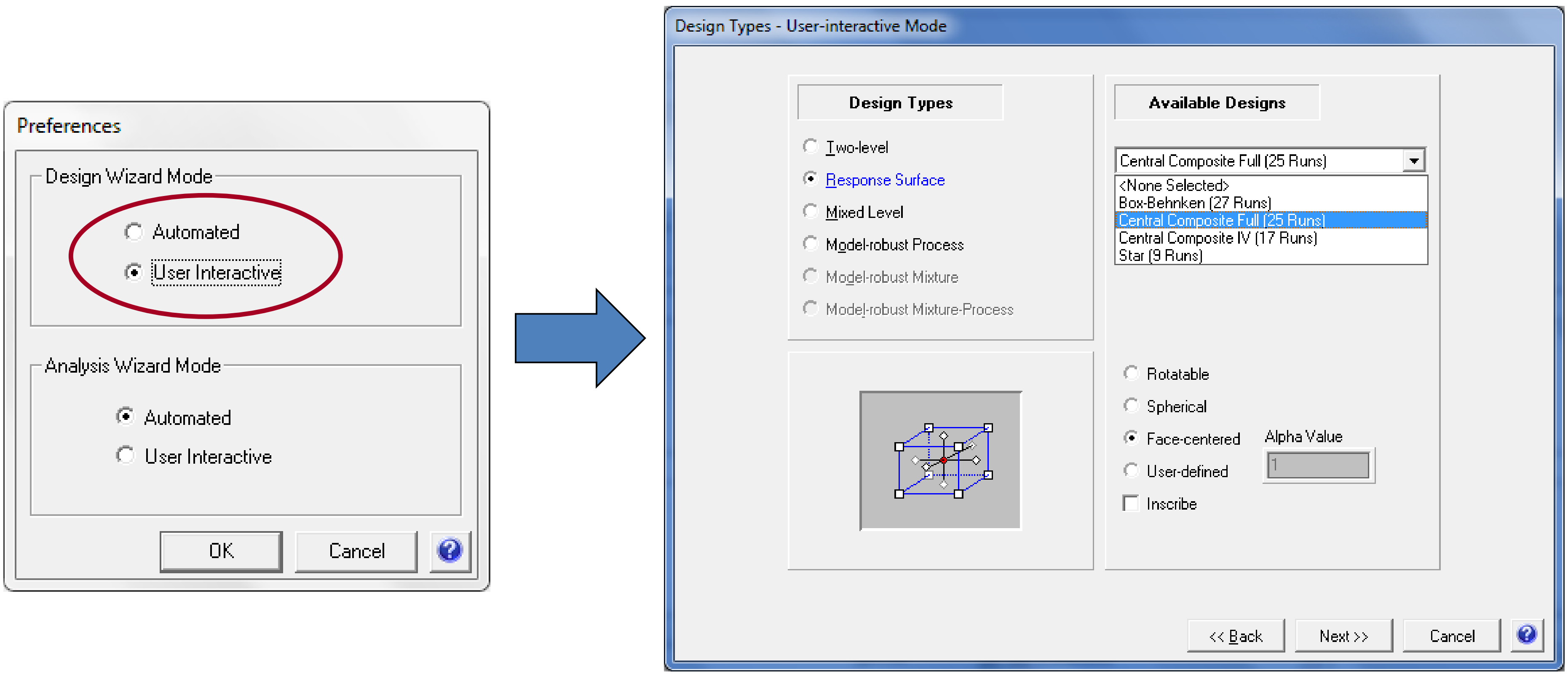
- Automated Mode – selects the most efficient design for you.



Automated DOE

Integrated DOE with Automated and User-interactive Design Modes

- User-interactive Mode – you select and tailor the design.



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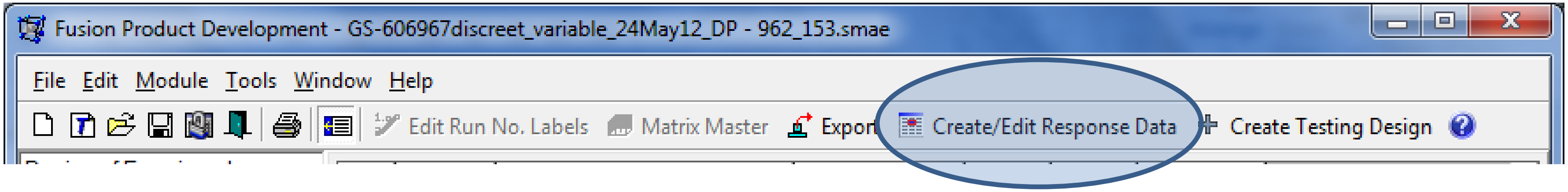
Feature 2 – Response Data Handler (RDH)

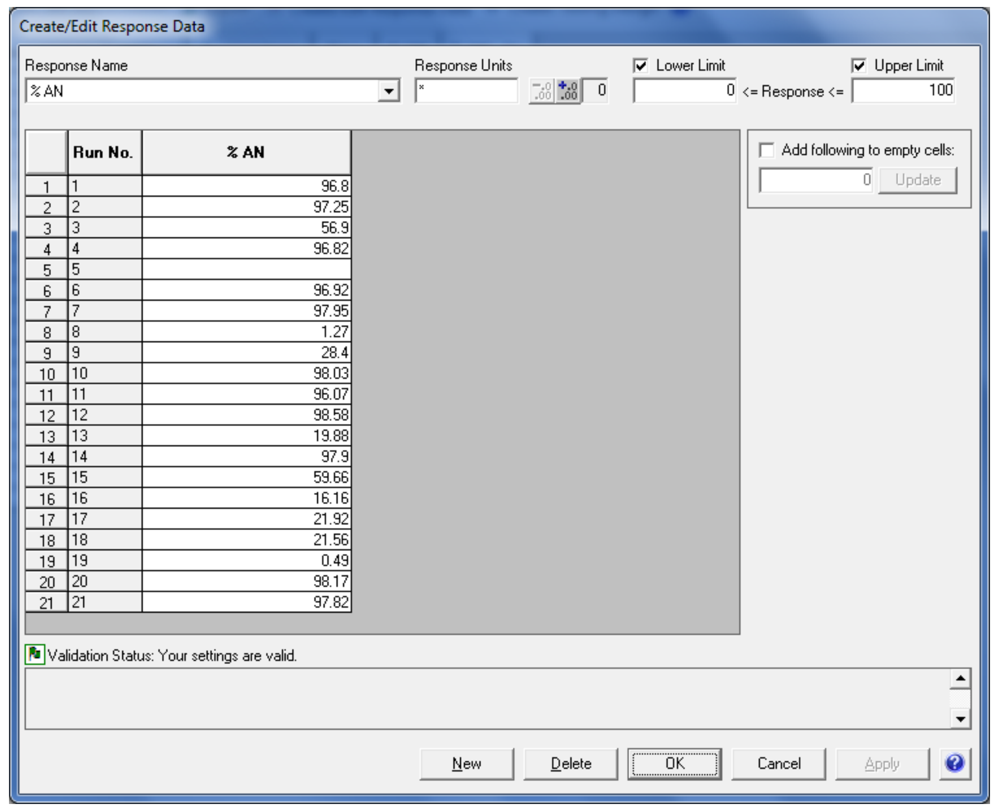
Handles Response Data Simply and Easily

- Single test result per run.
- Descriptive Statistics – multiple test results per run.
- Time Series – results at multiple time points per run.

Single Test Result Per Run



Responses consisting of only one measurement per run (no test repeats) can be entered directly onto the Experiment Design grid.



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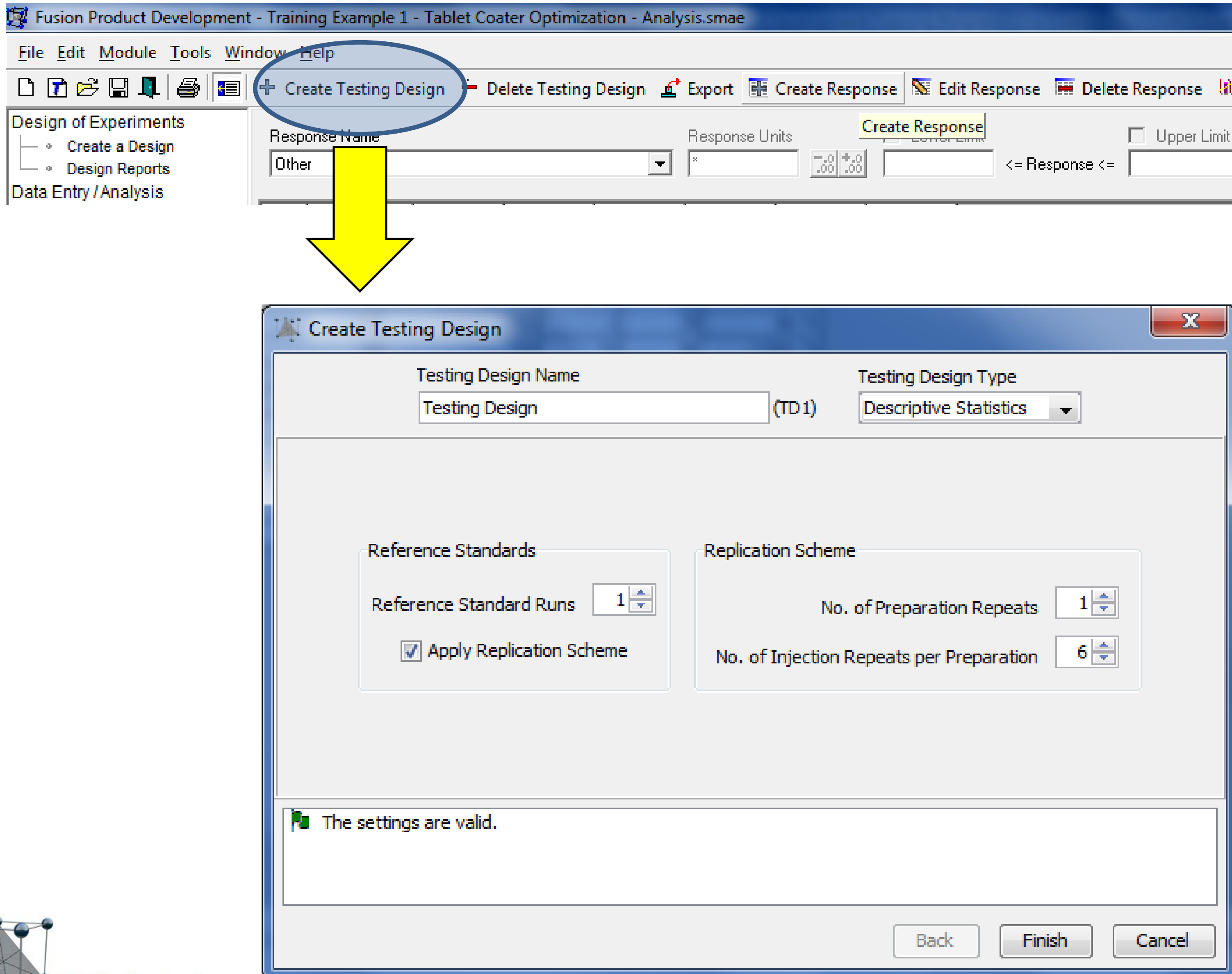
Descriptive Statistics – multiple test results per run



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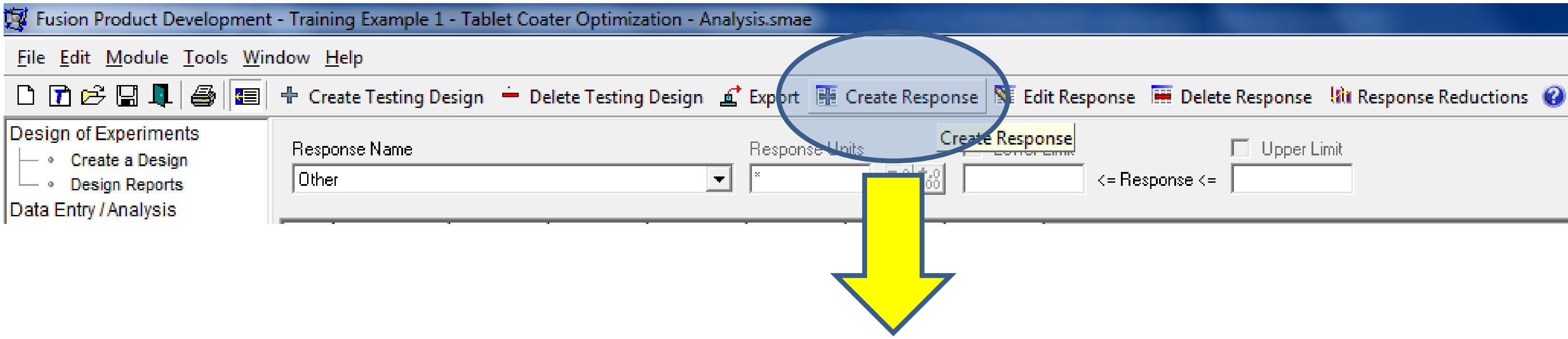
Descriptive Statistics – multiple test results per run



Response Name: Tablet Hardness
Response Units
Lower Lim

	A Run No.	B T1	C T2	D T3	E T4	F T5	G T6
1	1	74.06	76.54	75.02	73.74	75.84	75.87
2	2	75.12	75.65	75.43	74.33	74.86	75.03
3	3	78.21	76.77	77.71	77.06	77.22	75.94
4	4	77.40	77.48	74.95	76.61	74.78	76.17
5	5	76.03	76.49	75.89	74.86	75.49	75.14
6	6	75.61	75.10	75.82	76.74	75.74	75.55
7	7	74.18	76.21	73.48	73.66	73.34	74.56
8	8	73.30	76.92	76.36	77.03	76.29	75.55
9	9	75.01	75.46	75.75	72.41	75.13	74.01
10	10	76.14	74.79	76.62	75.92	74.71	74.94
11	11	74.04	73.62	74.68	73.80	76.26	74.73
12	12	75.26	74.14	74.32	75.79	74.07	74.14
13	13	74.20	73.44	75.19	74.39	74.53	74.53
14	14	73.63	75.07	77.09	76.65	76.45	76.45
15	15	77.64	74.14	73.64	75.30	74.28	77.58
16	16	77.50	79.23	76.42	76.74	75.88	77.74

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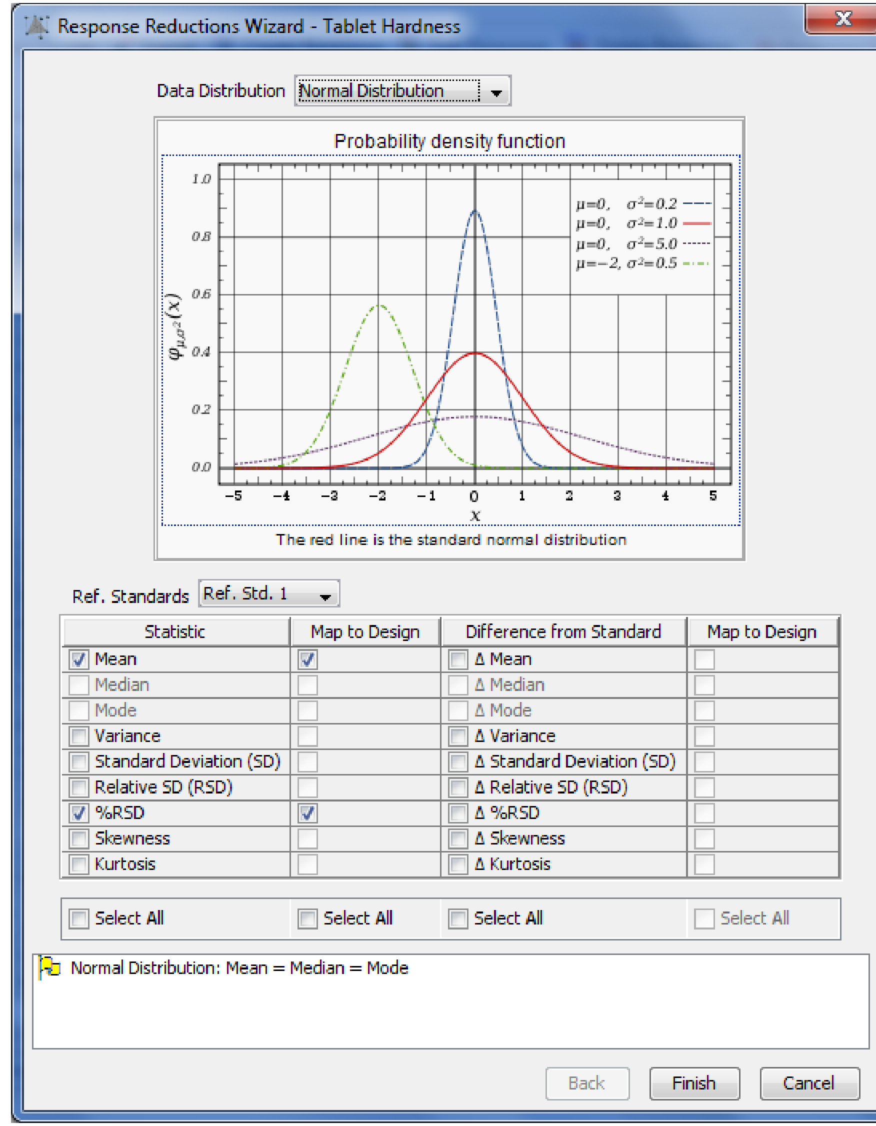
Descriptive Statistics – multiple test results per run

Can automatically:

- handle test repeat data
- handle non-normally distributed data
  - Log-normal
  - Exponential
  - Gamma
  - Weibull
- compute descriptive statistics based responses
- compute differences of all statistics from a reference standard
- map all computed responses to the experimental design for analysis



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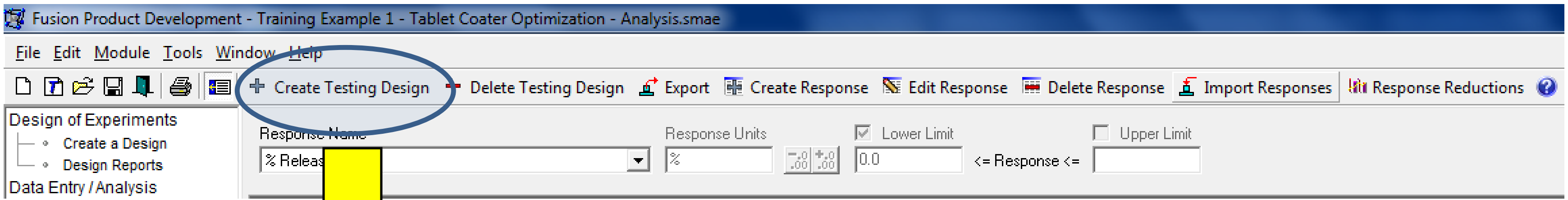
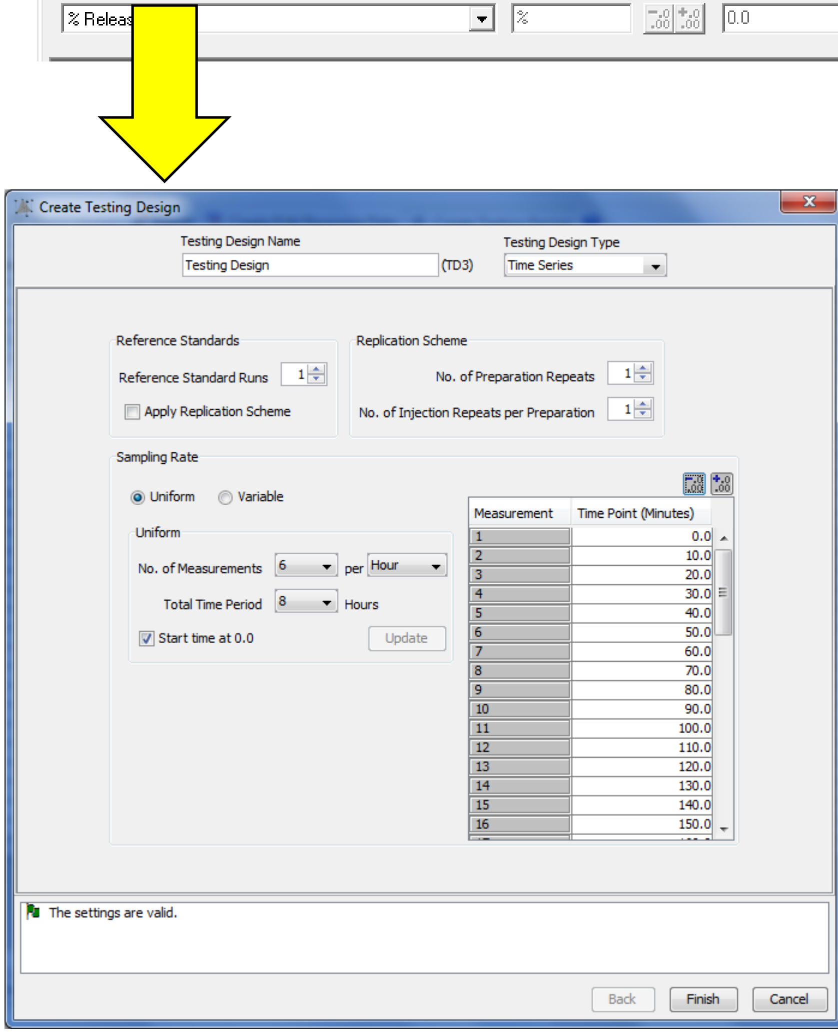
Time Series – results at multiple time points per run





Can automatically handle:

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

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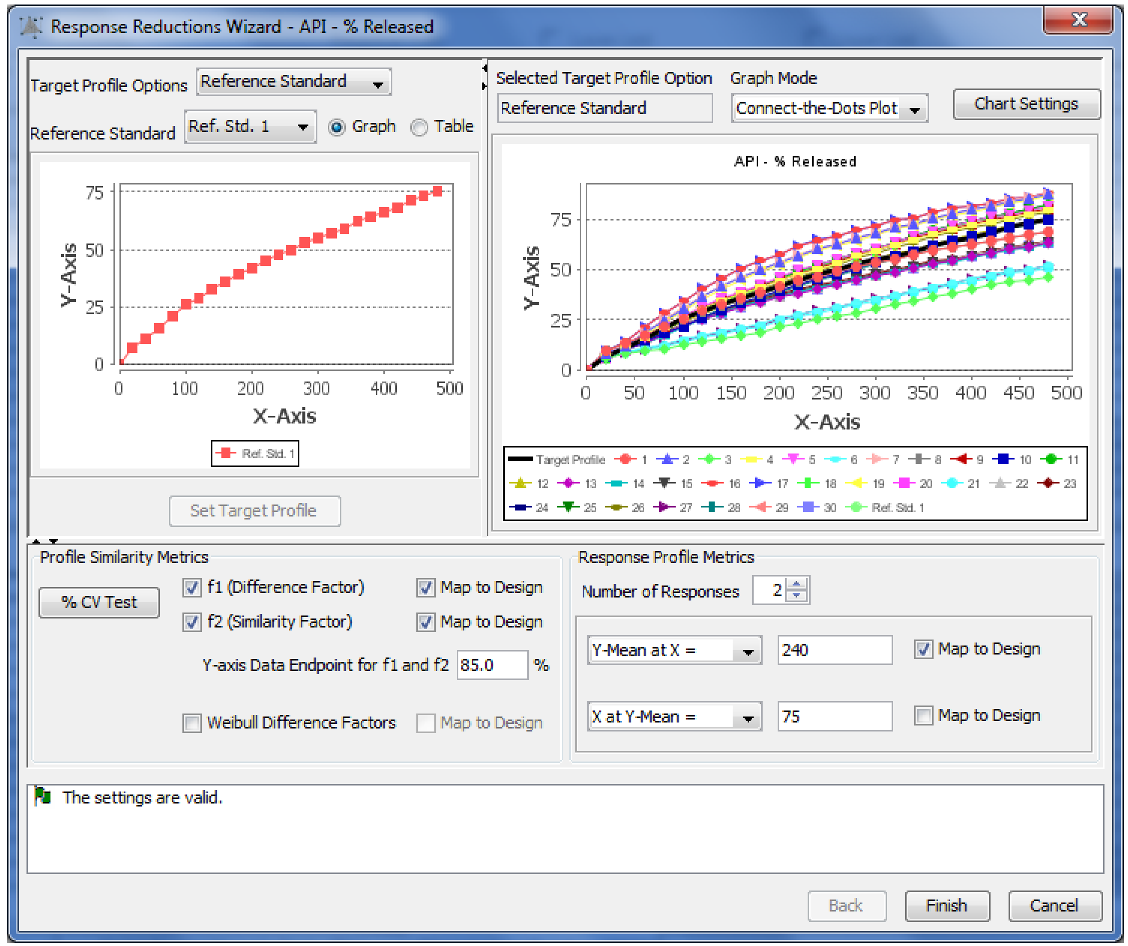
Time Series – results at multiple time points per run

Can automatically:

- handle test repeat data
- compute average profiles
- compute f1 & f2 curve fit metrics
- compute sensitive Weibull curve fit metrics
- compute additional profile response metrics
- Map all computed responses to the experimental design for analysis



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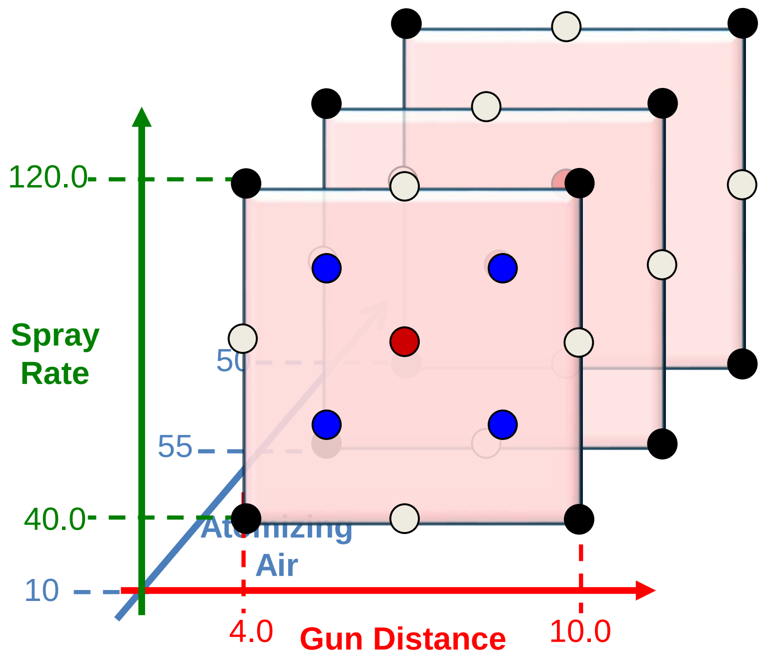
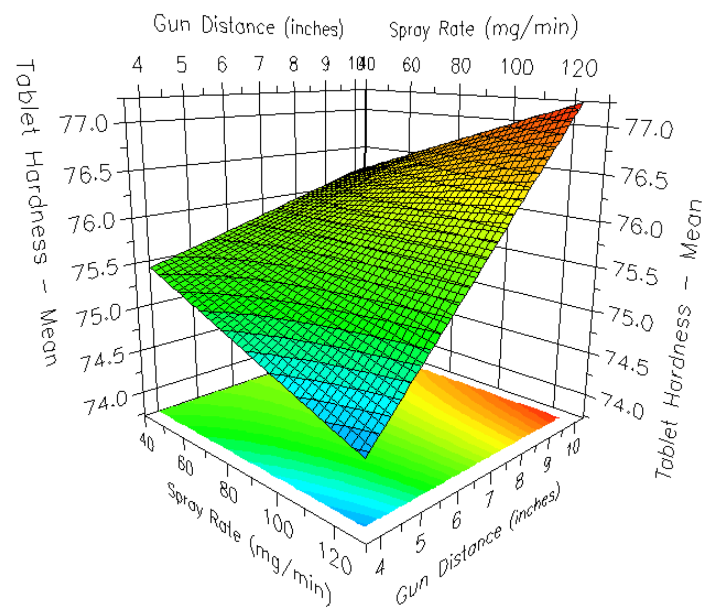
Feature 3 – Automated Analysis and Modeling

1. Statistical DOE runs – information rich data set.
2. Automated modeling generates a highly predictive and diagnostic model for each critical performance characteristic studied.





$$\text{Hardness} = 9.3 + 4.2(GD) - 5.4(SR)^2 + 12.7(AA)^2 + 1.3(PA*GD) + 1.6(SR)^2AA + \ldots$$

Linear Effects	Curvature Effects	Interaction Effects	Complex Effects

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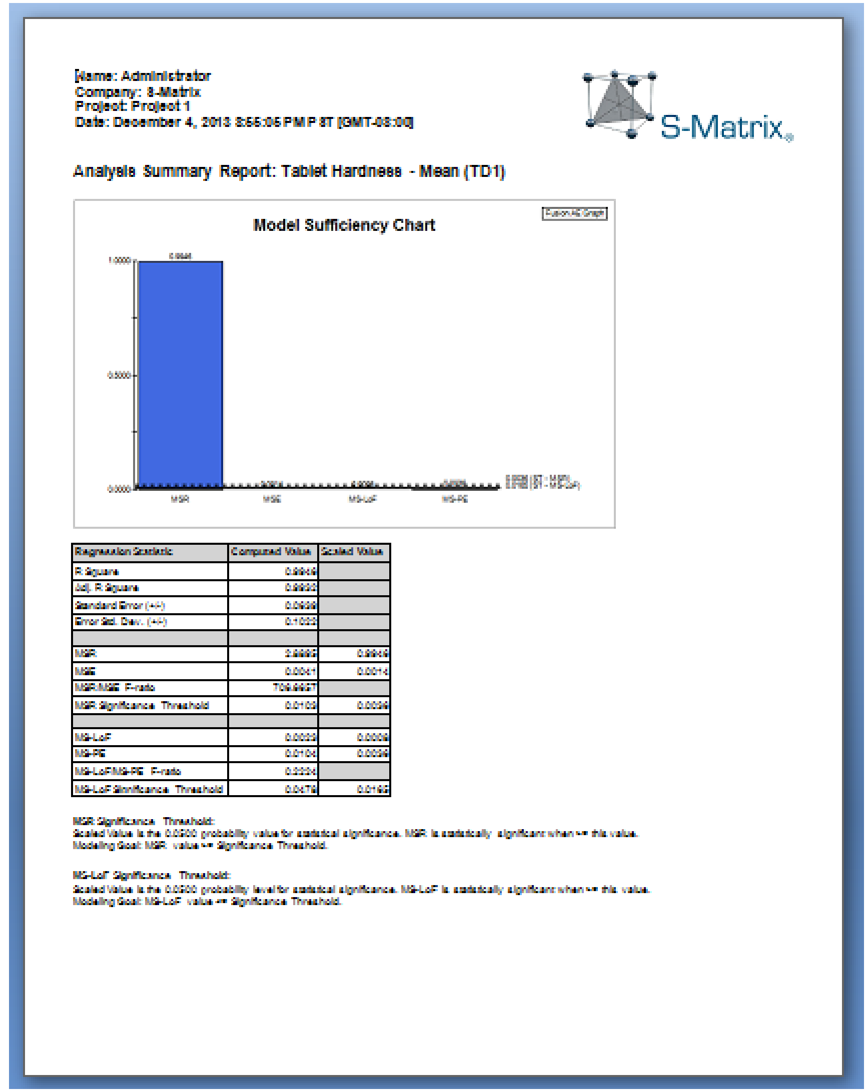
Automated Analysis and Modeling

Automated Modeling Includes:

- Error Analysis
- Regression Analysis
- Transformation Analysis
- Outlier Analysis

Instant Analysis Reports Include:

- Model Sufficiency Summary
- Analysis Detail Reports
  - Error Analysis
  - Regression Analysis
  - Residuals Report and Graphs
  - Transformation Analysis
  - Coefficients Table and Model
  - Mean Effects Report and Plot



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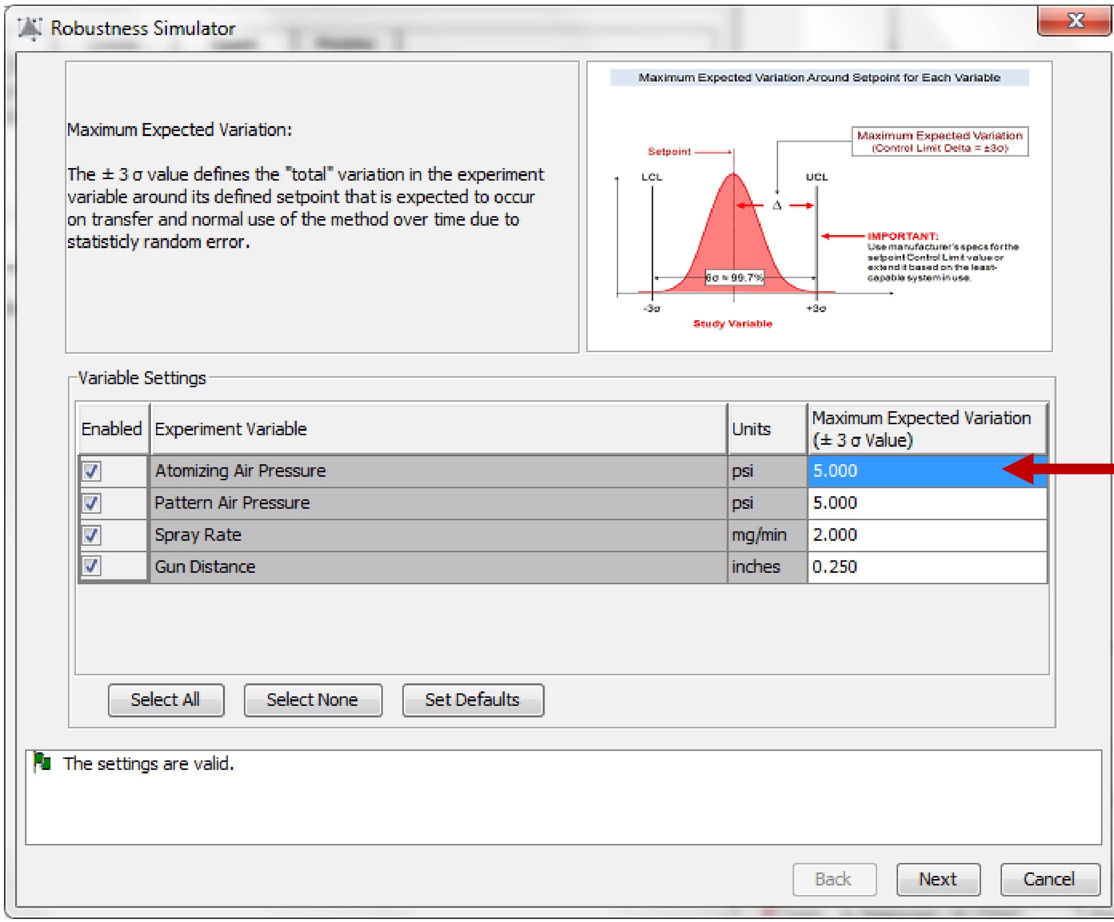
Feature 4 – Fully Integrated Robustness Simulation

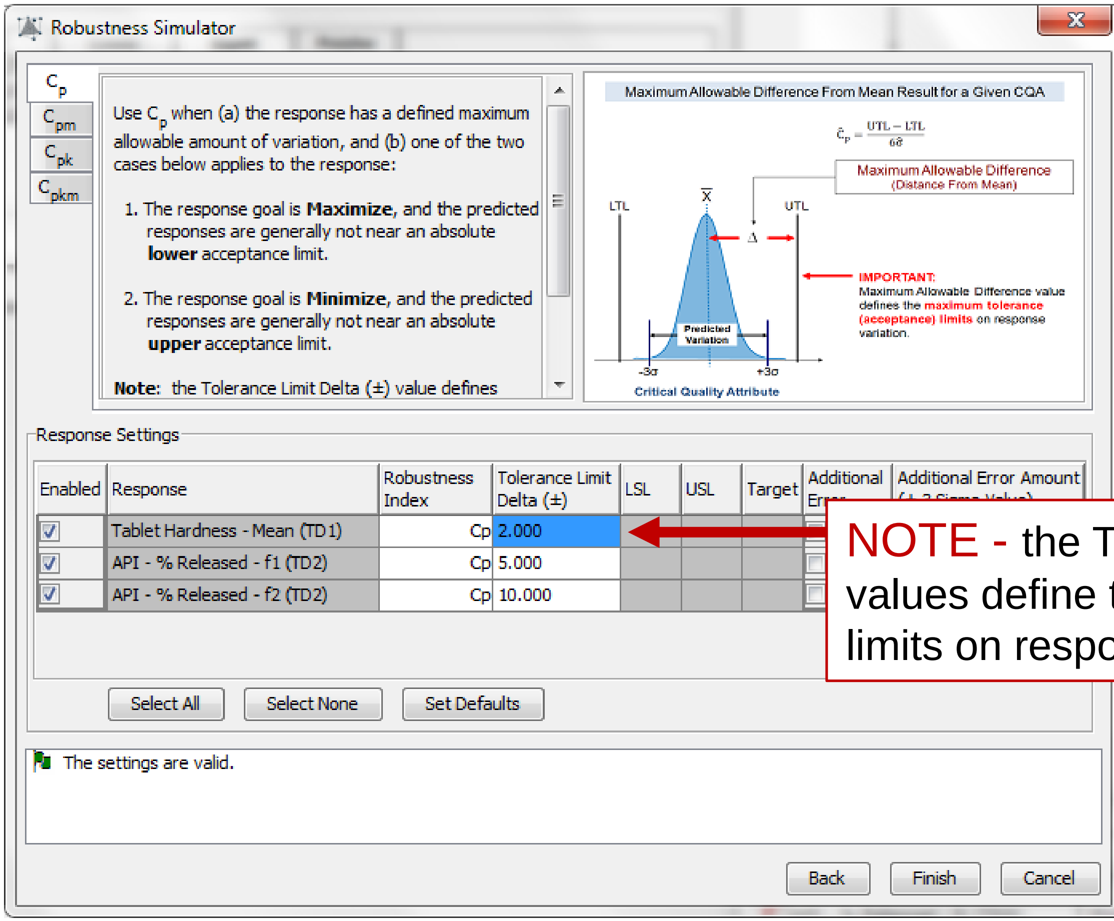
<u>Simultaneously optimize mean performance and robustness during development!</u>



NOTE - the value defines the maximum expected setpoint variation for the study factor.

Fully Integrated Robustness Simulation

Simultaneously optimize mean performance and robustness during development!



NOTE - the Tolerance Limit Delta values define the maximum allowable ± limits on response variation.

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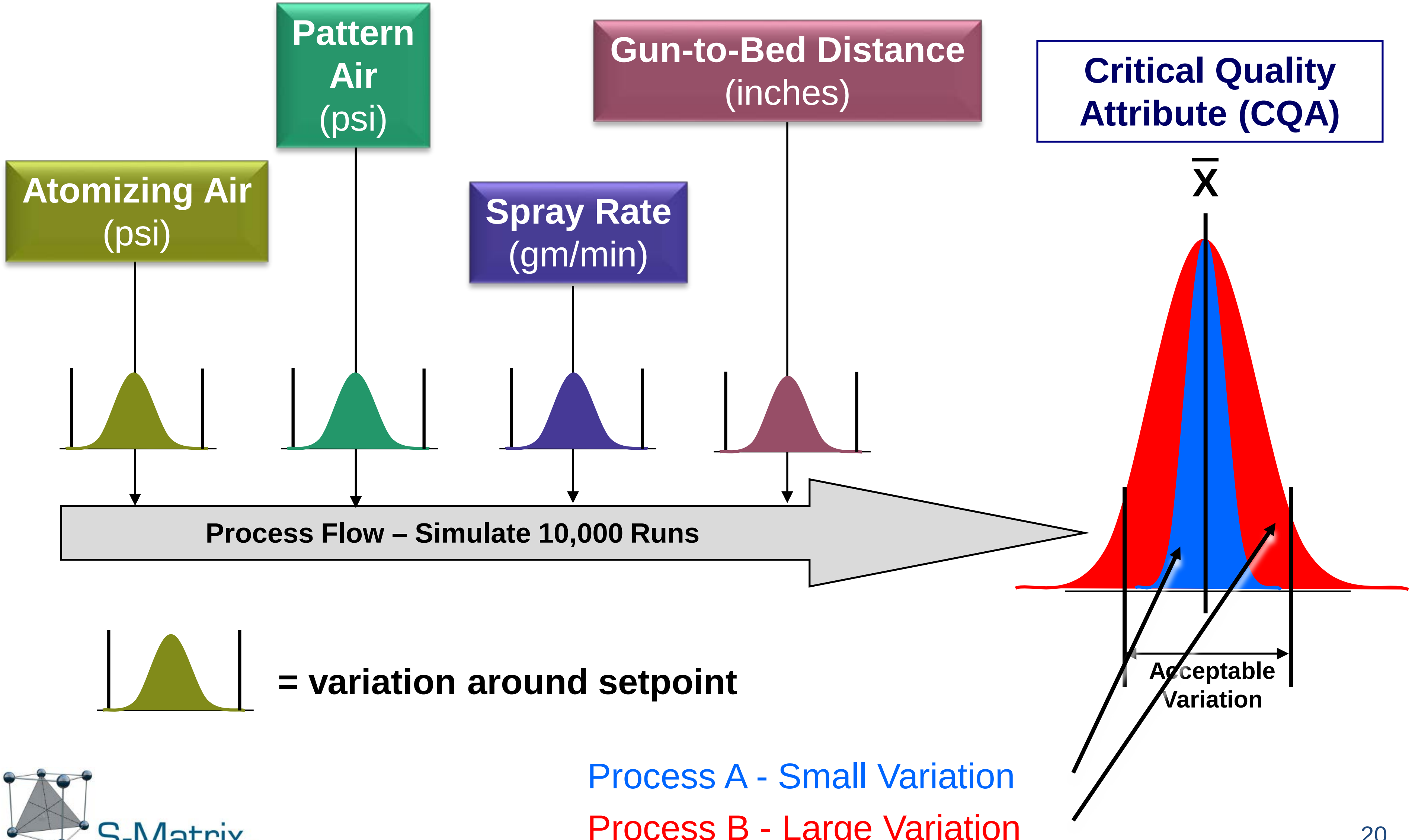
Fully Integrated Robustness Simulation

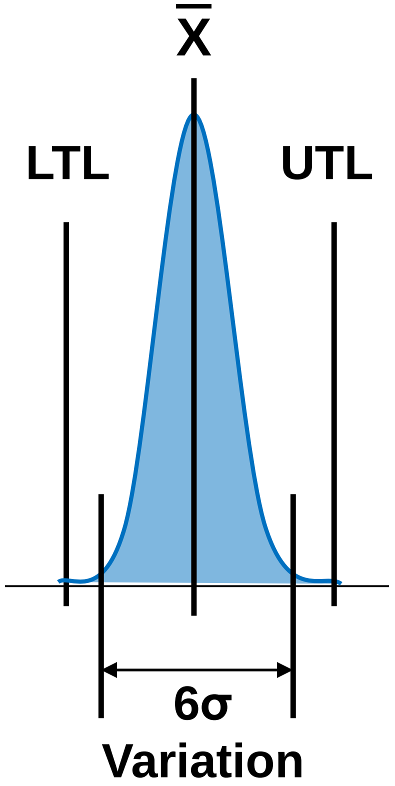


Process Capability - Quantified

Process Capability (**C_p**) – a direct, quantitative measure of process robustness used routinely in Statistical Process Control (SPC) applications. The classical SPC definition of "Inherent Process Capability" (C_p) is

$$C_p = \frac{UTL - LTL}{6\sigma \text{ variation}}$$

Critical Quality Attribute (CQA)



UTL and LTL = *Tolerance* Limits (tolerance width).

6σ Variation = ±3σ *process output variation*.

Traditional Goal ≥ 1.33

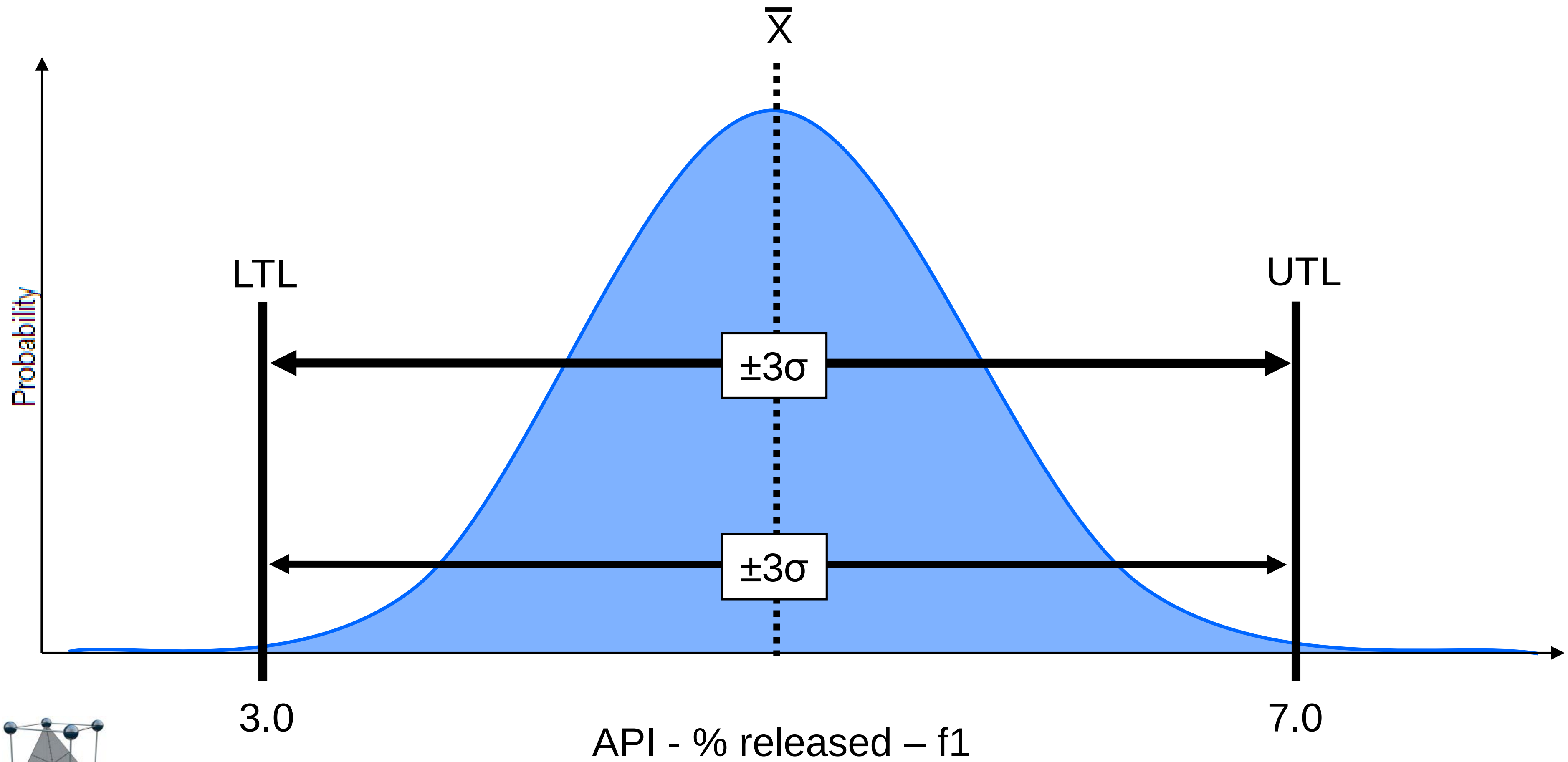
- based on setting the UTL and LTL at ±4σ of process performance variation.

- Note: a 6-sigma process would have a C_p = 2.00

Process Capability: Example Response = f1 (curve fit metric)

$$c_p = \frac{6\sigma}{6\sigma} = 1.00$$

±3σ Variation = Tolerance Limit Interval



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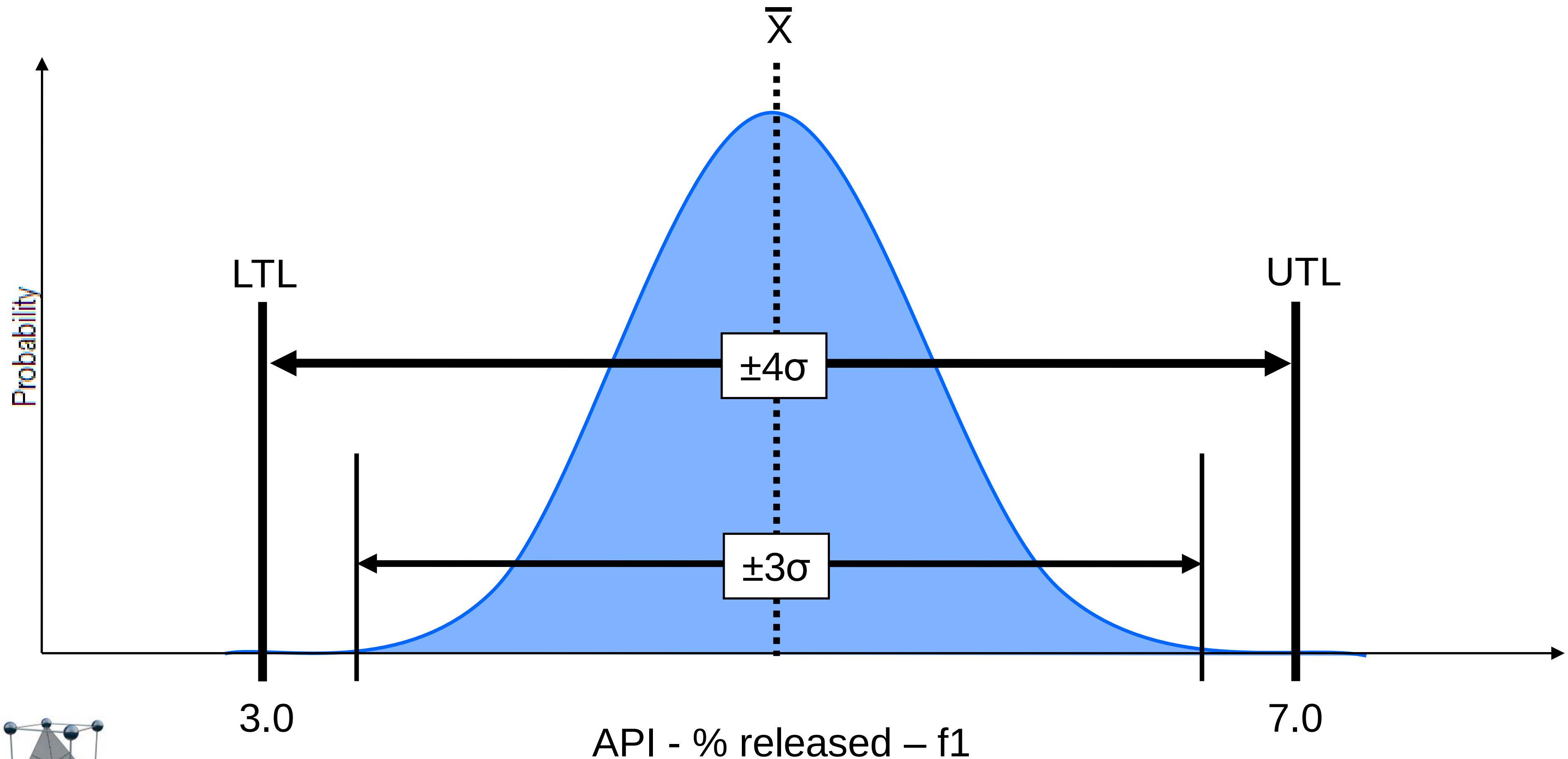
Process Capability: Example Response = f1 (curve fit metric)

$$c_p = \frac{8\sigma}{6\sigma} = 1.33$$

±3σ Variation = 75% of Tolerance Limit Interval



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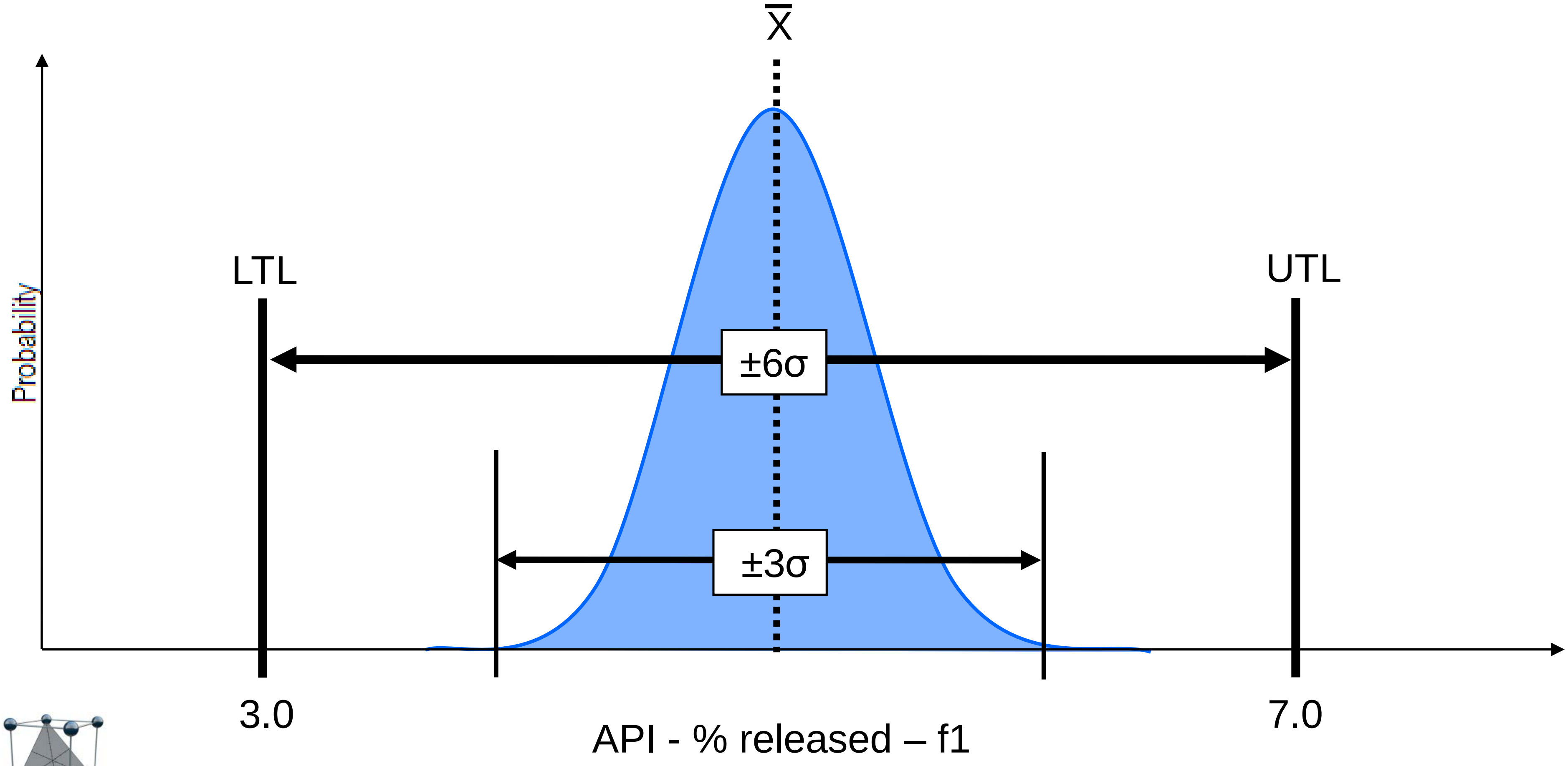
Process Capability: Example Response = f1 (curve fit metric)

$$c_p = \frac{12\sigma}{6\sigma} = 2.00$$

±3σ Variation = 50% of Tolerance Limit Interval

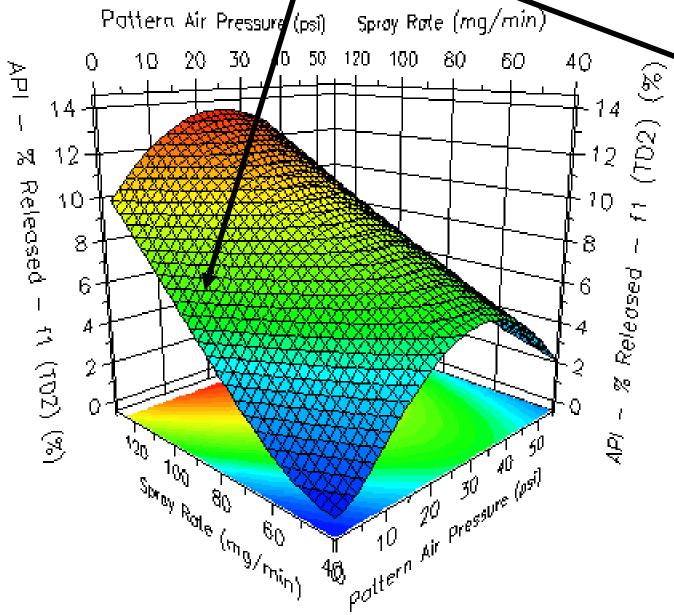


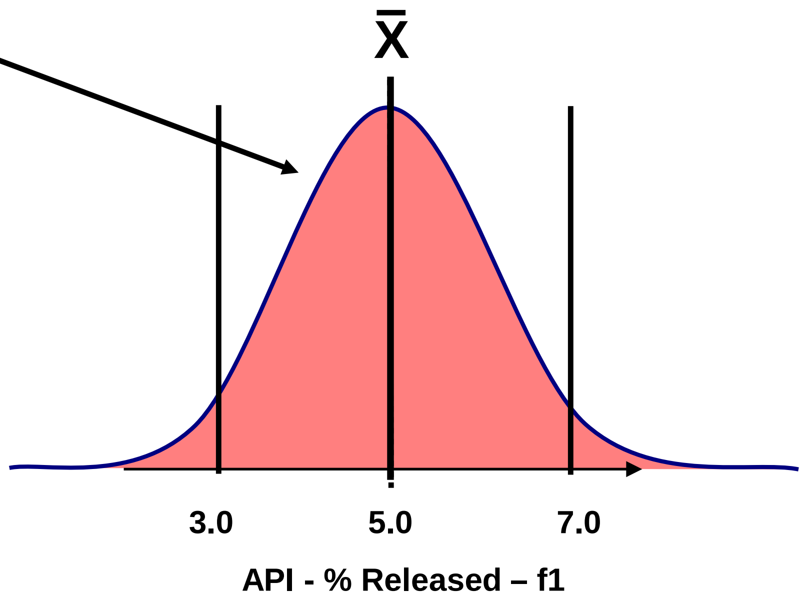
Fully Integrated Robustness Simulation

Simultaneously optimize mean performance and robustness during development!

With built in robustness metrics – no additional experiments are needed!

f1 = 5.00: Good Mean Performance
C_p < 1.00: Poor Robustness (steep slope)



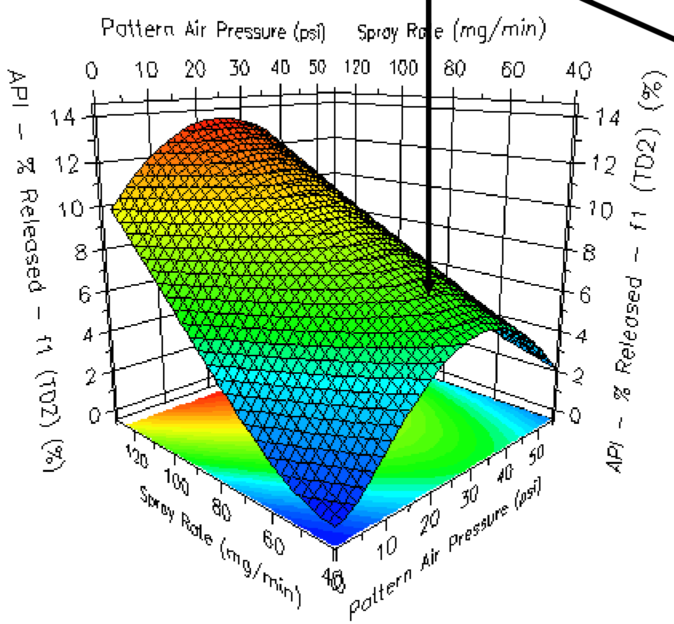


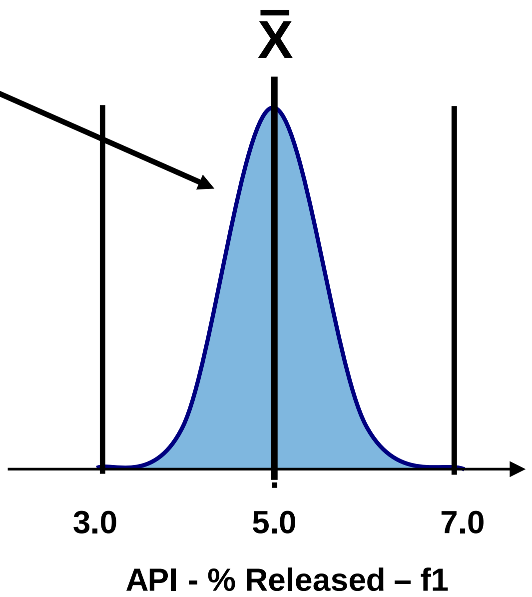
Fully Integrated Robustness Simulation

<u>Simultaneously optimize mean performance and robustness during development!</u>

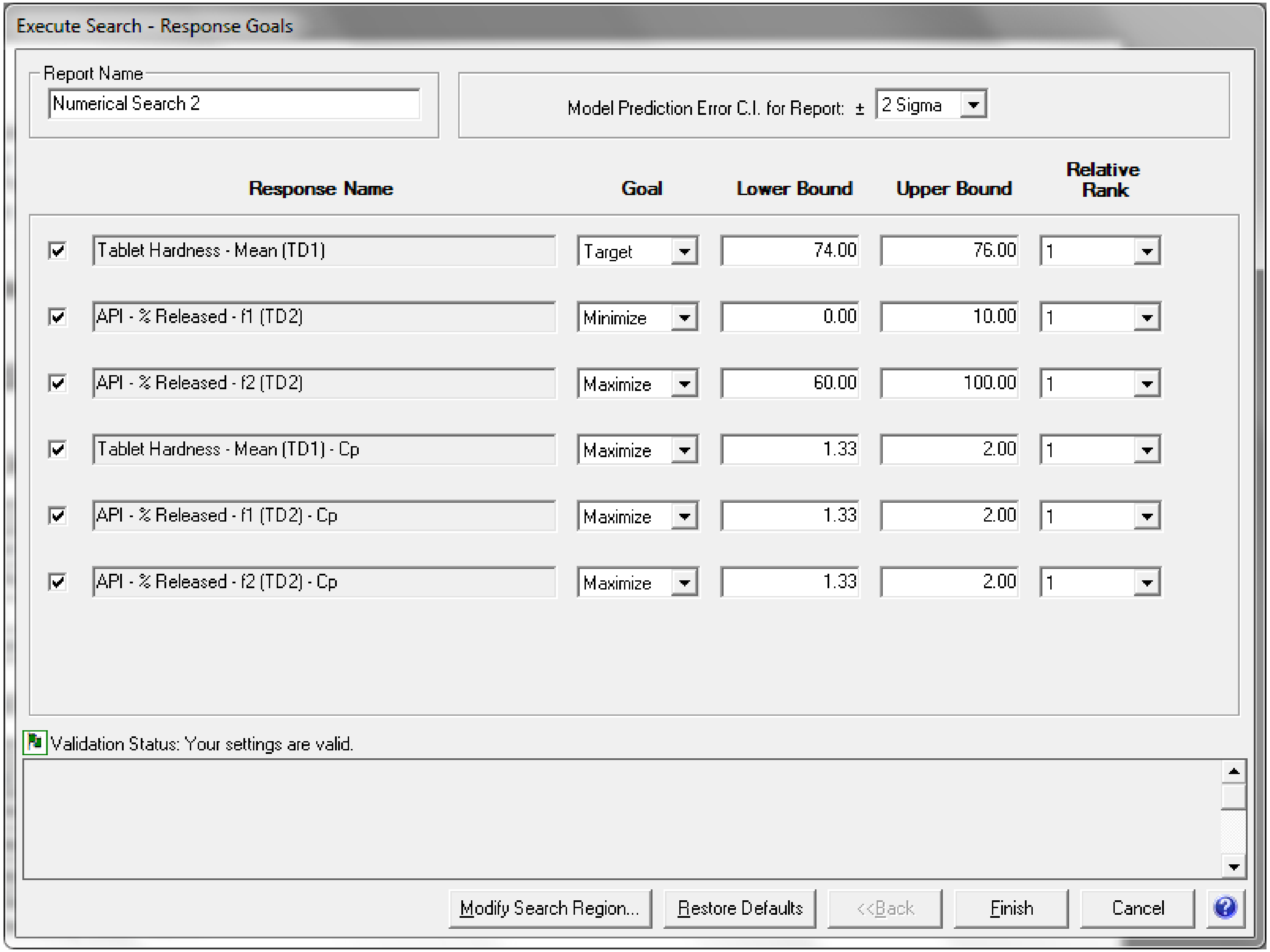
With built in robustness metrics – no additional experiments are needed!

f1 = 5.00: Good Mean Performance
C_p ≥ 1.33: Good Robustness (shallow slope)





Feature 5 – Best Answer Search Wizard



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Best Answer Search Wizard

Name: Administrator
Company: S-Matrix
Project: Project 1
Date: November 4, 2012 7:52:37 PM PST [GMT-08:00]

Numerical Search Results - Experiment 1

Answer #1

Variable Settings

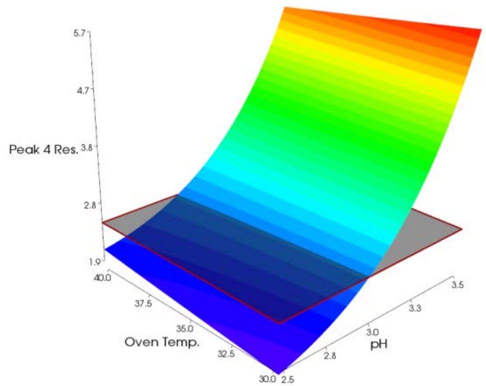
Variable	Level Setting
Atomizing Air Pressure	20.8
Pattern Air Pressure	55.0
Spray Rate	59.2
Gun Distance	8.8

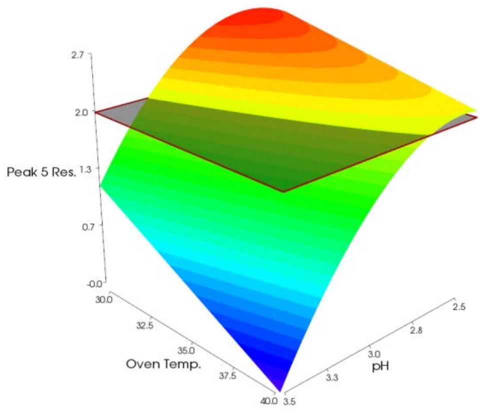
Predicted Results

Response	Goal	Predicted Result	Desirability	-2 Sigma Conf. Limit	+2 Sigma Conf. Limit
Tablet Hardness - Mean (TD1)	75.0	74.99	0.9887	74.85	75.13
Tablet Hardness - %RSD (TD1)	Minimize	1.64	0.6718	1.55	1.74
API - % Released - f1 (TD2)	Minimize	1.48	0.9016	0.71	2.51
API - % Released - f2 (TD2)	Maximize	87.23	0.7445	84.86	89.59

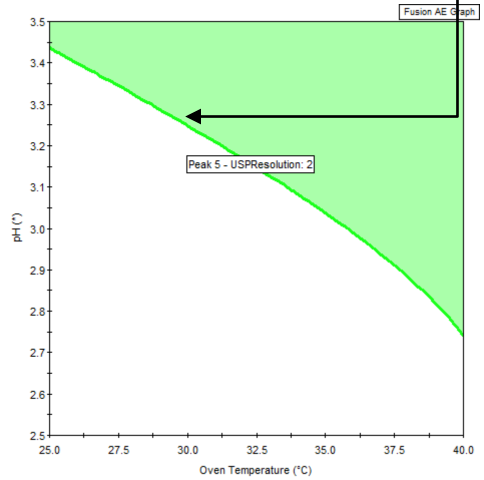
Cumulative Desirability Target = 1.0000
Cumulative Desirability Result = 0.8172

Feature 6 – Design and Operating Space Characterization

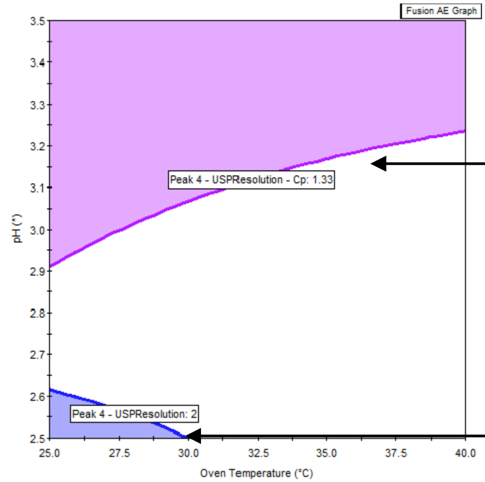




Edge of Failure – Mean Performance



Edges of Failure – Robustness



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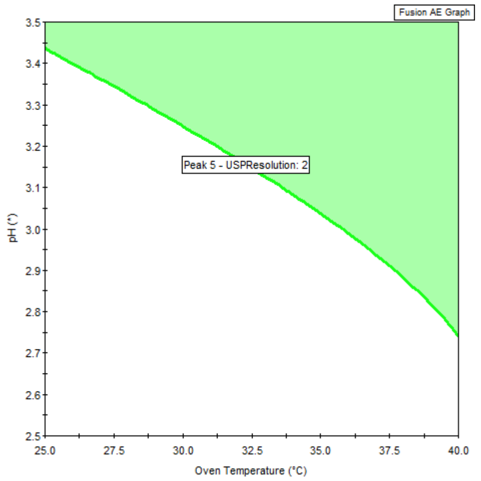
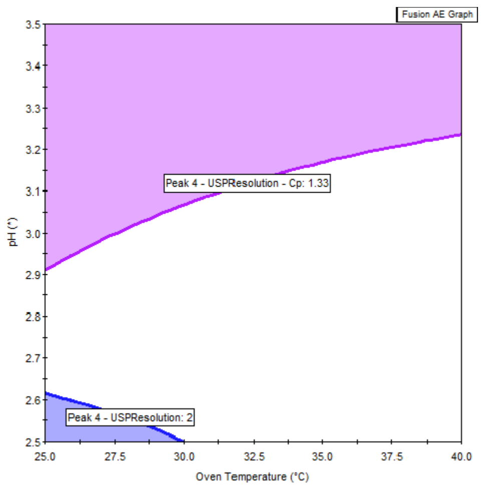
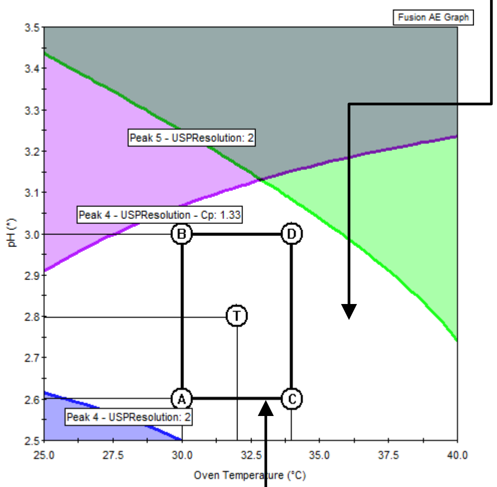
Design and Operating Space Characterization







Design Space –

joint region of acceptable mean performance ***and robustness***.

Operating Space –

Joint safe operating ranges of critical study parameters

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Design and Operating Space Characterization

Reports

O.S. - S.R. 60.0, G.D. 6.0

Graph Settings

	Name	Units	Lower Bound	Upper Bound	Pointer Coordinate
X	Atomizing Air Pressure	psi	10.0	50.0	
Y	Pattern Air Pressure	psi	0.0	55.0	

Spray Rate 60.0

Gun Distance 6.0

Verification Run Settings

☑ Include Bounded Operating Space

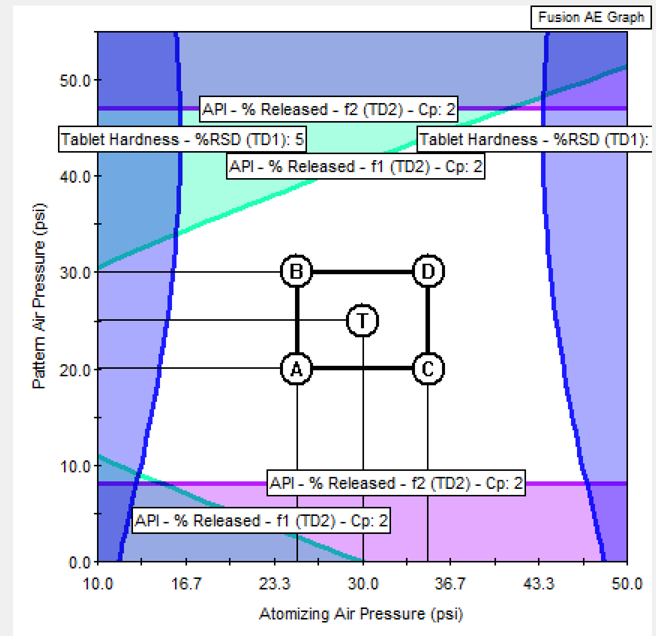
Operating Ranges

Variable	Lower Bound	Upper Bound	Center Point
Atomizing Air Pressure	25.0	35.0	30.0
Pattern Air Pressure	20.0	30.0	25.0

Verification Runs ☑ Show Verification Run Labels

Point	Run ID	Atomizing Air Pressure	Pattern Air Pressure	Spray Rate	Gun Distance
A	O.S._-_S.R._60.0	25.0	20.0	60.0	6.0
B	O.S._-_S.R._60.0	25.0	30.0	60.0	6.0
C	O.S._-_S.R._60.0	35.0	20.0	60.0	6.0
D	O.S._-_S.R._60.0	35.0	30.0	60.0	6.0
T	O.S._-_S.R._60.0	30.0	25.0	60.0	6.0

Graph



Response Settings

	Name	Goal	Lower Bound	Upper Bound	Target Predictions	Pointer Predictions	Contour Label	Color
☑	Tablet Hardness - Mean (TD1)	Target	74.00	76.00	74.70		☑	Red
☑	Tablet Hardness - %RSD (TD1)	Minimize		5.00	2.90		☑	Blue
☑	API - % Released - f1 (TD2)	Minimize		15.00	7.10		☑	Green
☑	API - % Released - f2 (TD2)	Maximize	50.00		70.71		☑	Orange

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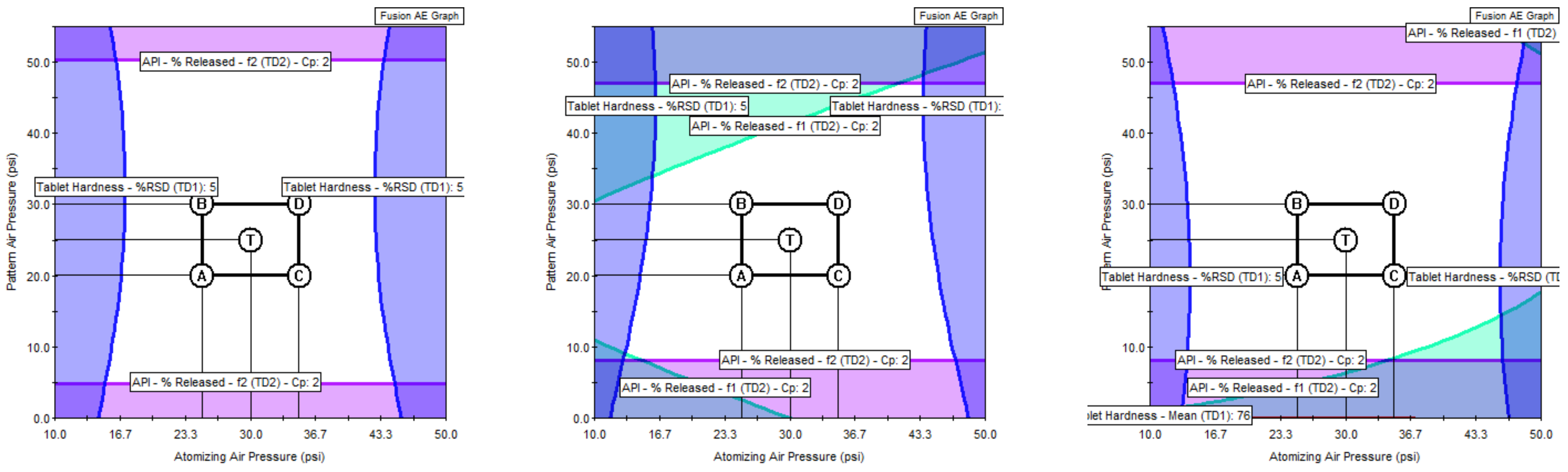
Design and Operating Space Characterization

- Acceptable Mean Performance – all performance characteriastics
- Acceptable Robustness – all performance characteriastics

3rd Factor = Low ← 3rd Factor at Setpoint → 3rd Factor = High



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Design and Operating Space Characterization

Tablet Coater Optimization Example

Reports

O.S. - S.R. 60.0, G.D. 7.0

Graph Settings

	Name	Units	Lower Bound	Upper Bound	Pointer Coordinate
X	Atomizing Air Pressure	psi	10.0	50.0	
Y	Pattern Air Pressure	psi	0.0	55.0	

Verification Run Settings

☑ Include Proven Acceptable Ranges (PARs)

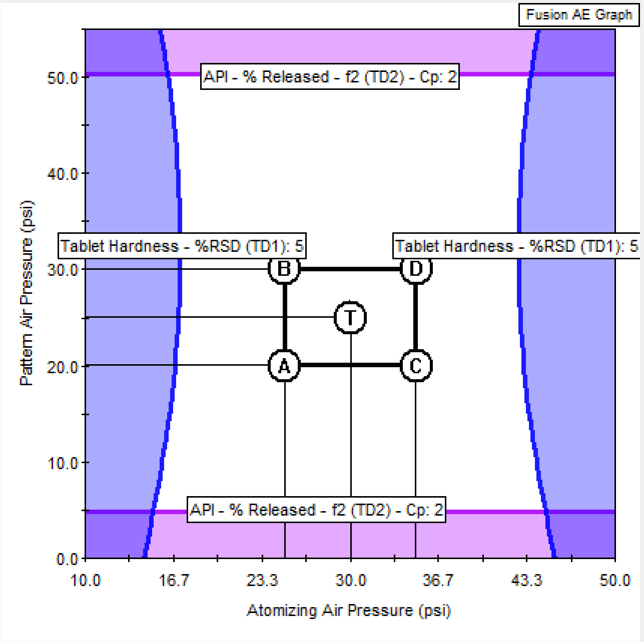
Operating Ranges

Variable	Lower Bound	Upper Bound	Center Point
Atomizing Air Pressure	25.0	35.0	30.0
Pattern Air Pressure	20.0	30.0	25.0

Verification Runs ☑ Show Verification Run Labels

Point	Run ID	Atomizing Air Pressure	Pattern Air Pressure	Spray Rate	Gun Distance
A	O.S._-_S.R._60	25.0	20.0	60.0	7.0
B	O.S._-_S.R._60	25.0	30.0	60.0	7.0
C	O.S._-_S.R._60	35.0	20.0	60.0	7.0
D	O.S._-_S.R._60	35.0	30.0	60.0	7.0
T	O.S._-_S.R._60	30.0	25.0	60.0	7.0

Graph



Response Settings

	Name	Goal	Lower Bound	Upper Bound	Target Predictions	Pointer Predictions	Contour Label	C
☑	Tablet Hardness - Mean (TD1)	Target	74.00	76.00	74.70		☑	Rec
☑	Tablet Hardness - %RSD (TD1)	Minimize		5.00	2.90		☑	Blu
☑	API - % Released - f1 (TD2)	Minimize		15.00	7.10		☑	Gre
☑	API - % Released - f2 (TD2)	Maximize	50.00		70.71		☑	Ora

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Design and Operating Space Characterization

Tablet Coater Optimization Example

Reports

Trellis - D.S. + PARs — Generate Preview

	Axis Variable	Units	Lower Bound	Upper Bound
X	Atomizing Air Pressure (A)	psi	10.0	50.0
Y	Pattern Air Pressure (B)	psi	0.0	55.0

	Horizontal Trellis Variable: Spray Rate (C)	Vertical Trellis Variable: Gun Distance (D)
Low Level	55.0	6.0
Medium Level	60.0	7.0
High Level	65.0	8.0

Verification Run Settings

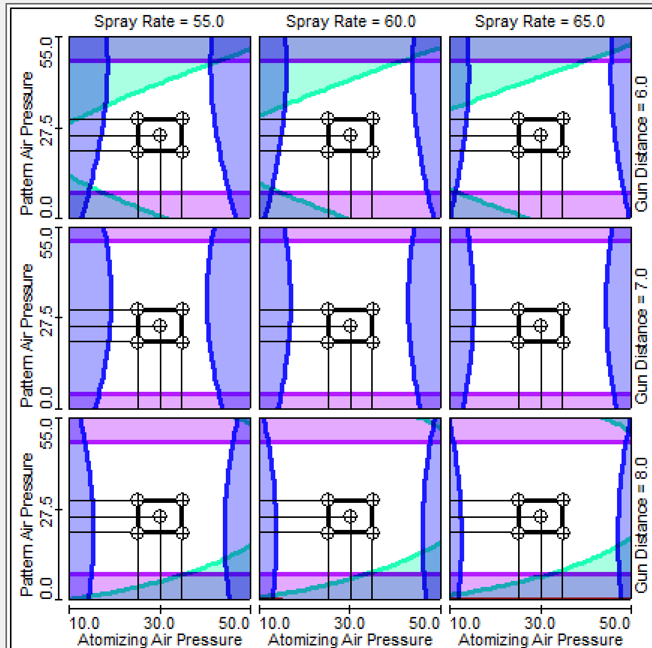
☑ Include Proven Acceptable Ranges (PARs)

Operating Ranges

Variable	Lower Bound	Upper Bound	Center Point
Atomizing Air Pressure	25.0	35.0	30.0
Pattern Air Pressure	20.0	30.0	25.0

Verification Runs

Graph



Response Settings

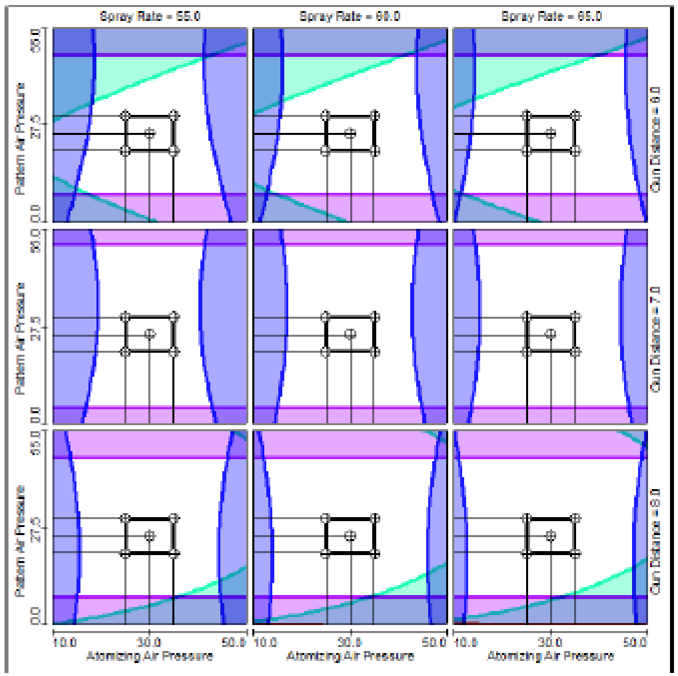
Name	Goal	Lower Bound	Upper Bound	Color
API - % Released - f1 (TD2)	Minimize		15.00	Green
API - % Released - f2 (TD2)	Maximize	50.00		Orange
API - % Released - f1 (TD2) - Cp	Maximize	2.00		Teal
API - % Released - f2 (TD2) - Cp	Maximize	2.00		Purple

S-Matrix®

Final Report → Output file formats include Word and PDF

Name: Administrator
Company: S-Matrix Corporation
Project: Project 1
Date: November 17, 2013 4:11:45 AM PST [GMT-08:00]

Overlay Graphics - Trellis - D.S. + PARs



Operating Space Settings

Axis	Name	Lower Bound	Upper Bound	Centerpoint
X	Atomizing Air Pressure	25.0	35.0	30.0
Y	Pattern Air Pressure	20.0	30.0	25.0

Verification Runs

Point	Run ID	Atomizing Air Pressure	Pattern Air Pressure	Spray Rate	Gun Distance
A	Trellis_-_D.S._+_PARs_A1_A	25.0	20.0	55	6
B	Trellis_-_D.S._+_PARs_A1_B	25.0	30.0	55	6

Conclusions

The Fusion Pro QbD-based Approach:

- ✓ **Greatly accelerates successful R&D through:**
  - **Automation**
  - **Statistically valid experimentation**
  - **Novel data treatments**
- ✓ **Provides quantitative knowledge of all critical parameter effects**
- ✓ **Enables establishing Design Space for both:**
  - **Mean Performance (setpoint optimization)**
  - **Process Robustness (operating space)**
- ✓ **Required time for the work is dramatically reduced**
- ✓ **Success promotes further the use of QbD**

Fusion Pro – QbD-aligned R&D Software

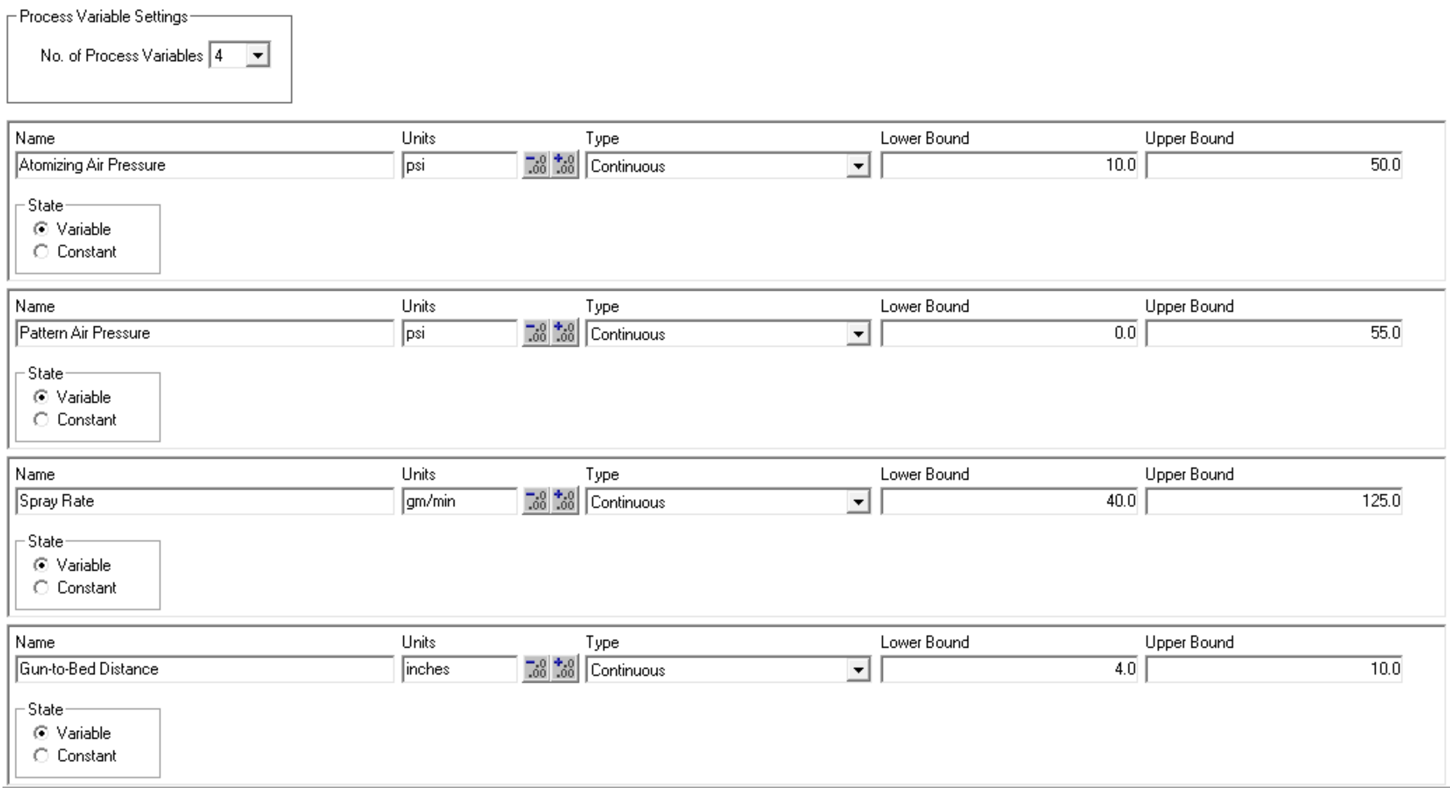
Case Study 1 –

Tablet Coating Process

Case Study 1 – Tablet Coating Process

The experiment was undertaken to optimize a tablet coating process for several critical tablet quality characteristics. The two which will be discussed in this case study are Hardness and Dissolution (% Released profile).

The four critical process parameters (CPPs) selected for study are entered into the Experiment Setup template shown below.



Process Variable Settings

No. of Process Variables: 4

Name	Units	Type	Lower Bound	Upper Bound	State
Atomizing Air Pressure	psi	Continuous	10.0	50.0	Variable
Pattern Air Pressure	psi	Continuous	0.0	55.0	Variable
Spray Rate	gm/min	Continuous	40.0	125.0	Variable
Gun-to-Bed Distance	inches	Continuous	4.0	10.0	Variable

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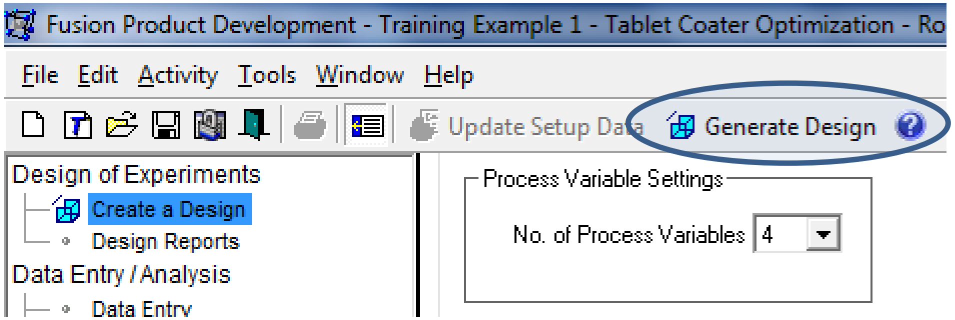
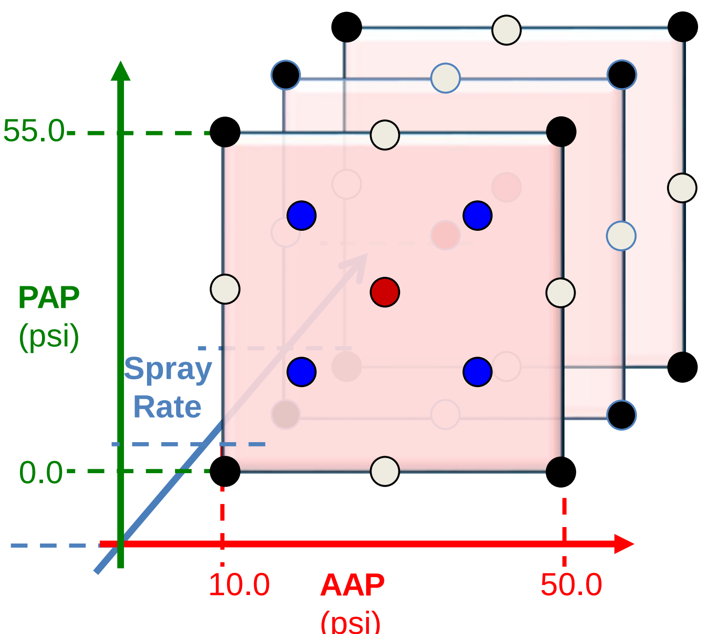
Automated Experiment Design Generation



One Click:

Software maps the experimental design to the study factors.



	Run No.	Atomizing Air Pressure	Pattern Air Pressure	Spray Rate	Gun-to-Bed Distance
1	1	30	55	82.5	7
2	2	30	27.5	82.5	10
3	3	50	0	125	10
4	4	10	0	40	10
5	5	10	55	125	10
6	6	10	55	40	4
7	7	30	27.5	82.5	4
8	8	30	0	82.5	7
9	9	50	55	40	10
10	10	50	0	40	4
11	11	30	27.5	82.5	7
12	12	10	55	40	10
13	13	10	0	125	4
14	14	50	55	40	4
15	15	10	0	40	4
16	16	10	0	125	10
17	17	50	55	125	10
18	18	50	27.5	82.5	7
19	19	50	0	40	10
20	20	30	27.5	82.5	7
21	21	10	55	125	4
22	22	50	55	125	4
23	23	10	0	40	4
24	24	10	27.5	82.5	7
25	25	30	27.5	82.5	7
26	26	30	27.5	40	7
27	27	10	55	40	4
28	28	50	0	125	4
29	29	50	0	40	4
30	30	30	27.5	125	7

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Generate Design – Statistical Efficiency

5 levels of Atomizing Air Pressure

5 levels of Pattern Air Pressure

5 levels of Spray Rate

5 levels of Gun-to-Bed Distance

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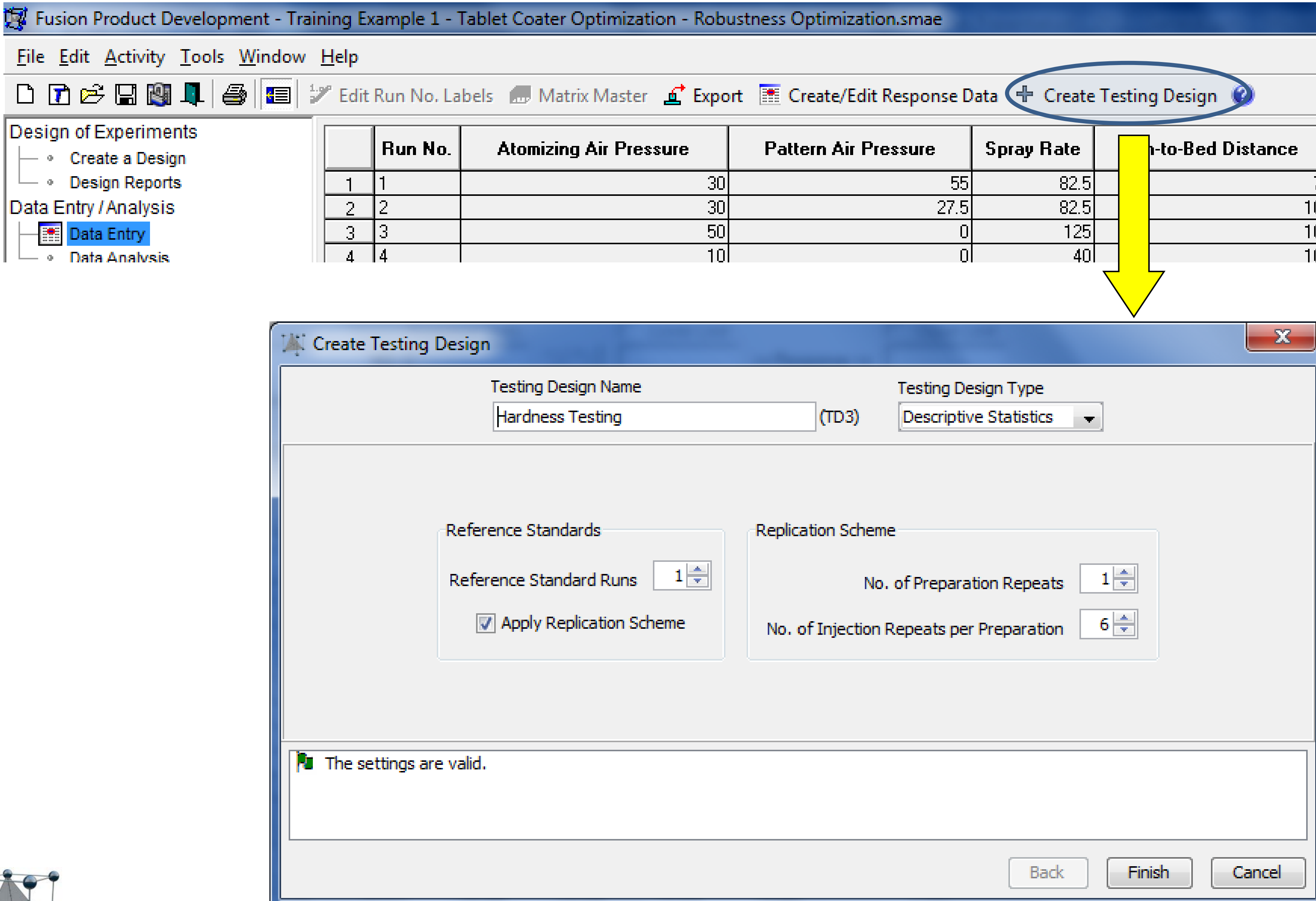
5 x 5 x 5 x 5 = 625 possible combinations

Fusion Screening design = 25 runs (excluding replicates)

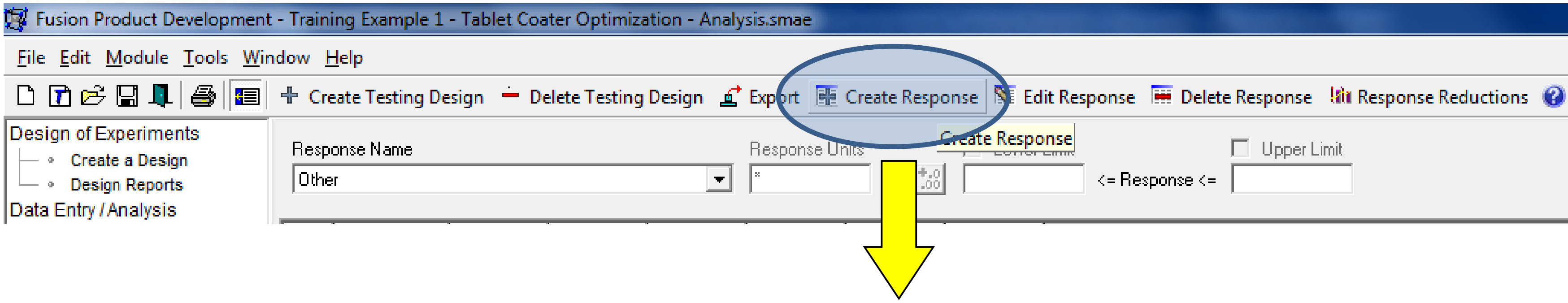
~ 25x efficiency.

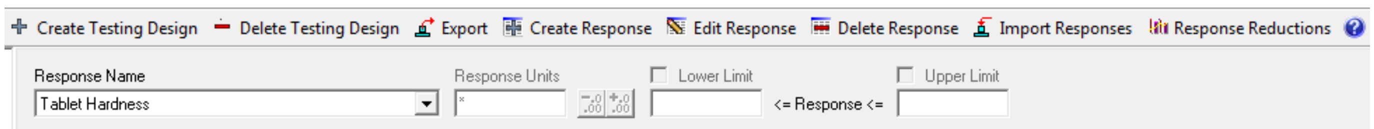
Create Testing Design – Hardness Testing.



S-Matrix®

Testing Design Data Entry – Hardness Data





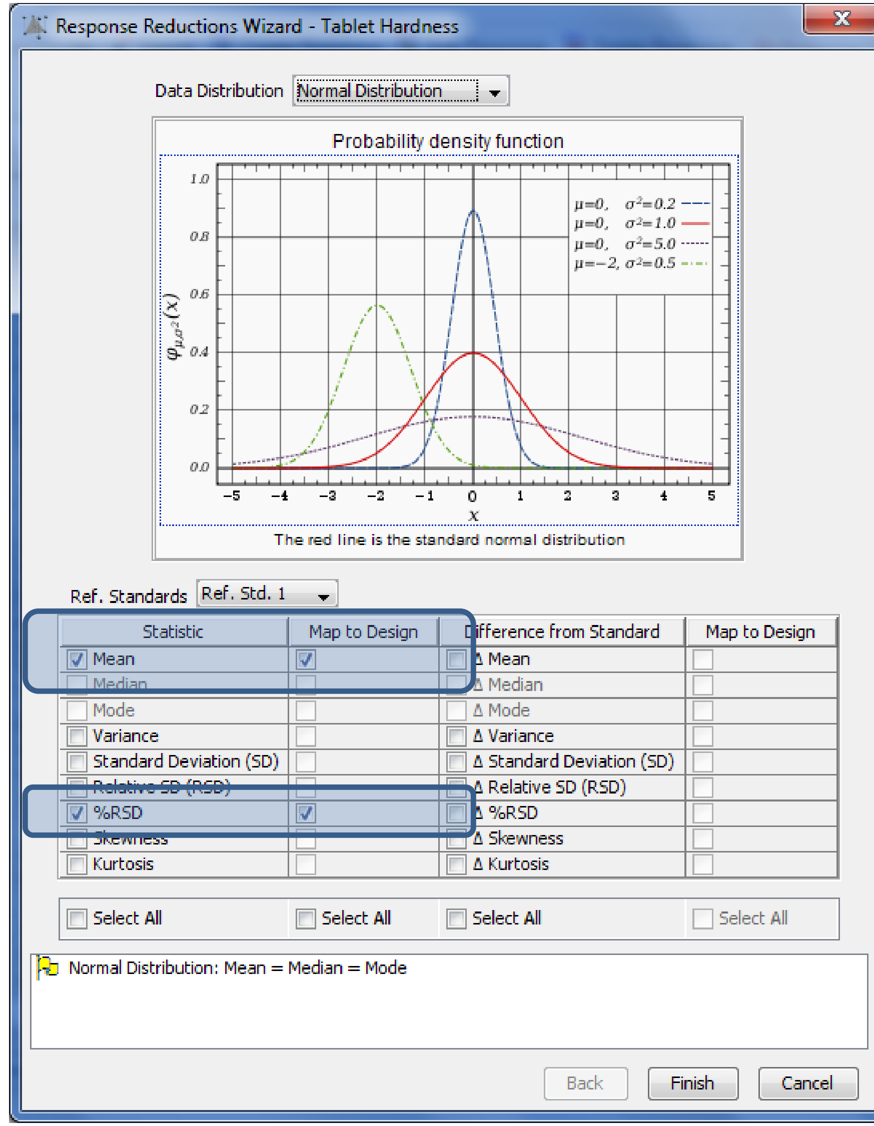
	A Run No.	B T1	C T2	D T3	E T4	F T5	G T6	H Mean	I %Relative SD
1	1	75.17	73.58	76.52	74.24	77.53	74.03	75.18	2.07
2	2	74.00	74.91	75.54	76.06	75.56	74.36	75.07	1.05
3	3	63.26	97.04	70.56	91.25	80.56	60.20	77.15	19.48
4	4	77.95	74.44	76.59	78.30	72.76	77.34	76.23	2.87
5	5	73.72	77.89	77.63	74.23	73.75	76.70	75.65	2.60
6	6	57.40	64.80	66.89	97.75	81.26	86.48	75.76	20.14
7	7	73.53	75.25	74.77	74.55	74.38	72.97	74.24	1.13
8	8	73.31	75.80	75.49	77.99	77.21	75.65	75.91	2.13
9	9	75.57	72.96	76.27	74.75	75.00	73.22	74.63	1.75
10	10	73.94	76.16	75.98	78.49	73.00	75.54	75.52	2.53
11	11	72.83	74.20	73.11	75.54	77.17	74.25	74.52	2.17
12	12	73.95	74.20	76.63	72.85	75.56	74.51	74.62	1.77
13	13	73.51	74.50	74.31	73.47	77.01	73.47	74.38	1.84
14	14	86.94	84.70	58.27	94.76	68.53	62.12	75.89	19.63
15	15	78.06	74.09	73.21	77.15	75.86	74.20	75.43	2.54
16	16	85.36	82.40	98.92	75.92	61.19	59.71	77.25	19.45
17	17	76.01	75.93	75.75	72.73	74.17	78.67	75.54	2.65
18	18	81.81	62.77	72.72	90.73	74.98	65.08	74.68	14.00
19	19	78.98	75.17	78.01	74.28	73.33	76.60	76.06	2.88
20	20	73.84	76.88	72.62	75.97	73.90	75.42	74.77	2.12
21	21	78.80	72.94	74.89	73.38	75.43	73.14	74.76	2.97
22	22	72.80	74.50	72.19	74.54	77.43	77.40	74.81	2.97
23	23	75.02	79.38	74.41	74.23	74.75	74.77	75.43	2.59
24	24	74.06	88.17	58.73	76.27	70.29	80.55	74.68	13.30
25	25	72.40	74.02	75.39	73.94	75.25	77.21	74.70	2.19
26	26	83.55	74.56	59.33	82.56	73.55	74.64	74.70	11.64
27	27	57.36	76.21	67.38	98.40	69.36	86.93	75.94	19.42

S-Matrix®

Response Data Reductions – Hardness Data

Software automatically:

- handles test repeat data
- handles non-normally distributed data
    - Log-normal
    - Exponential
    - Gamma
    - Weibull
- computes descriptive statistics based responses
- computes differences of all statistics from a reference standard
- Maps all computed responses to the experimental design for analysis



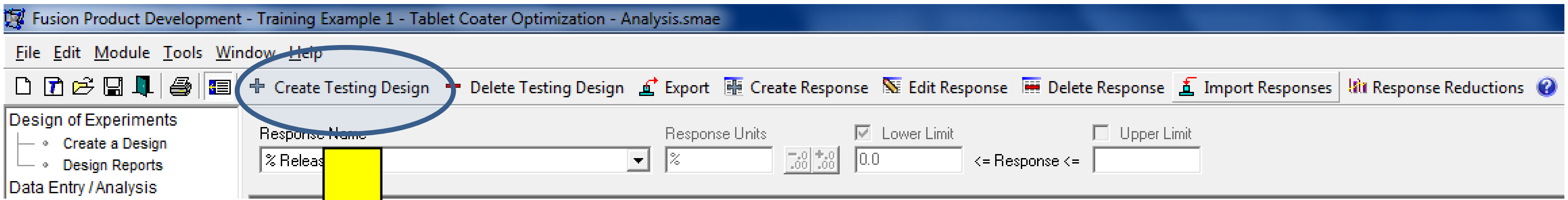
S-Matrix®

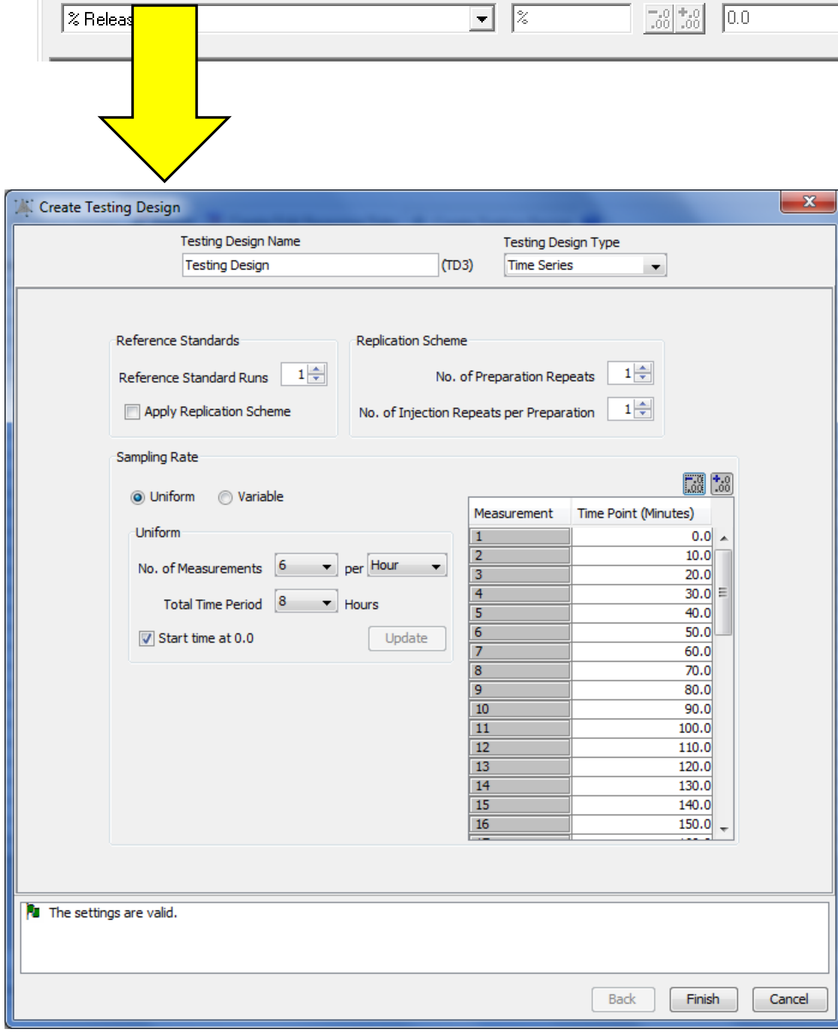
Response Data Reductions – Hardness Data

	Run No.	Atomizing Air Pressure	Pattern Air Pressure	Spray Rate	Gun Distance	Tablet Hardness - Mean (TD1)	Tablet Hardness - %RSD (TD1)
1	1	30	55	82.5	7	75.18	1.47
2	2	30	27.5	82.5	10	75.07	0.61
3	3	50	0	125	10	77.15	1.01
4	4	10	0	40	10	76.23	1.53
5	5	10	55	125	10	75.65	0.80
6	6	10	55	40	4	75.76	0.71
7	7	30	27.5	82.5	4	74.24	1.44
8	8	30	0	82.5	7	75.91	1.82
9	9	50	55	40	10	74.63	1.66
10	10	50	0	40	4	75.52	1.07
11	11	30	27.5	82.5	7	74.52	1.29
12	12	10	55	40	10	74.62	0.97
13	13	10	0	125	4	74.38	0.76
14	14	50	55	40	4	75.89	1.71
15	15	10	0	40	4	75.43	2.35
16	16	10	0	125	10	77.25	1.54
17	17	50	55	125	10	75.54	0.89
18	18	50	27.5	82.5	7	74.68	1.34
19	19	50	0	40	10	76.06	1.42
20	20	30	27.5	82.5	7	74.77	1.61
21	21	10	55	125	4	74.76	0.91
22	22	50	55	125	4	74.81	1.52
23	23	10	0	40	4	75.43	0.77
24	24	10	27.5	82.5	7	74.68	1.02
25	25	30	27.5	82.5	7	74.70	0.93
26	26	30	27.5	40	7	74.70	1.15
27	27	10	55	40	4	75.94	1.52
28	28	50	0	125	4	74.39	1.69
29	29	50	0	40	4	75.46	1.43
30	30	30	27.5	125	7	74.59	1.58

S-Matrix®

Create Testing Design – Time Series (Dissolution) Testing.

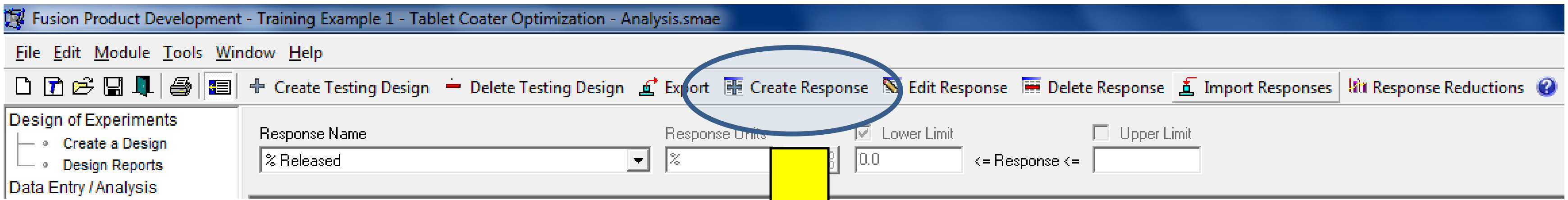




Software automatically handles:

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

Create Testing Design – Import Test Results From the CDS.

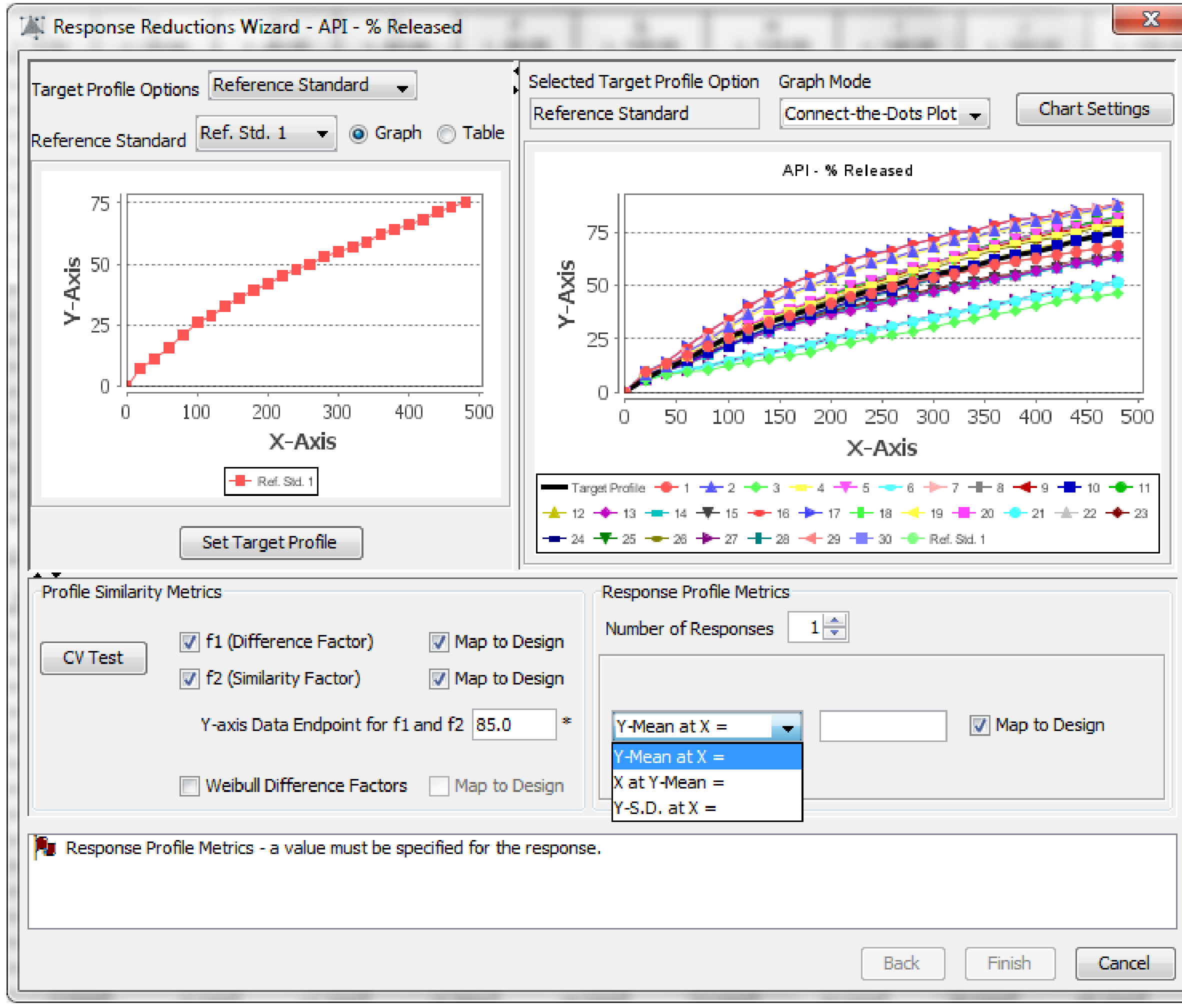


	A Run No.	B t - 0.00	C t - 20.00	D t - 40.00	E t - 60.00	F t - 80.00	G t - 100.00	H t - 120.00	I t - 140.00	J t - 160.00	K t - 180.00	L t - 200.00	M t - 220.00	N t - 240.00
1	1.a	0.00	9.50	13.30	17.20	21.10	25.60	29.50	32.30	35.40	38.80	41.40	44.20	46.50
2	1.b	0.00	9.40	13.50	17.60	21.60	25.40	29.60	32.80	35.60	38.30	41.50	44.90	46.50
3	1.c	0.00	9.50	13.60	17.80	21.80	25.50	29.40	32.40	35.40	38.30	41.60	44.60	46.50
4	1.d	0.00	9.80	13.60	17.70	21.30	25.50	29.90	32.50	35.50	38.40	41.30	44.50	46.40
5	1.e	0.00	9.20	13.40	17.40	21.50	25.70	29.30	32.60	35.50	38.60	41.60	44.30	46.70
6	1.f	0.00	9.60	13.60	17.30	21.70	25.30	29.30	32.40	35.60	38.60	41.60	44.50	46.40
7	2.a	0.00	8.20	12.00	18.50	24.60	30.60	36.50	41.80	45.80	50.00	53.70	57.00	60.70
8	2.b	0.00	7.60	12.40	18.30	24.70	30.90	36.90	41.40	46.10	50.00	53.60	57.10	60.60
9	2.c	0.00	7.90	12.30	18.50	24.80	31.20	36.70	41.60	46.50	50.30	53.50	57.30	60.50
10	2.d	0.00	8.10	12.00	18.20	24.80	30.40	36.00	41.40	46.00	50.10	53.20	57.00	60.50
11	2.e	0.00	8.40	12.00	18.40	25.30	31.20	36.30	41.40	46.10	49.90	53.80	57.10	60.50
12	2.f	0.00	7.80	12.50	18.50	25.20	31.10	36.60	41.40	46.10	50.30	53.20	57.10	60.20
13	3.a	0.00	5.70	8.50	9.30	10.20	12.70	14.60	15.60	17.40	18.90	21.60	23.40	25.10
14	3.b	0.00	6.00	8.70	9.60	10.90	12.50	14.30	15.20	17.10	19.00	21.70	23.60	25.00
15	3.c	0.00	5.80	8.30	9.20	10.20	12.80	14.10	15.50	17.00	18.90	21.90	23.50	25.10
16	3.d	0.00	5.90	8.60	9.30	10.00	12.70	14.30	15.90	17.10	18.60	21.70	23.40	24.90
17	3.e	0.00	6.00	8.40	9.30	10.70	12.40	14.20	15.40	17.10	18.70	22.00	23.40	25.00
18	3.f	0.00	6.00	8.50	9.70	10.40	12.50	14.30	15.40	17.50	18.70	21.90	23.10	25.50
19	4.a	0.00	7.50	11.60	16.30	20.80	26.40	30.70	34.50	38.00	40.90	44.60	47.40	50.40
20	4.b	0.00	7.10	11.40	16.00	21.30	25.90	30.70	34.10	38.00	41.10	44.50	47.70	50.20
21	4.c	0.00	7.50	11.10	16.50	21.00	26.20	30.20	34.70	38.30	41.50	44.70	47.20	50.00
22	4.d	0.00	7.60	11.70	15.90	21.30	26.10	30.40	34.40	38.20	40.60	44.30	47.50	50.00
23	4.e	0.00	7.60	11.30	15.90	21.00	25.90	30.40	34.60	38.20	41.30	44.40	47.60	50.00
24	4.f	0.00	7.10	11.30	16.00	21.20	26.10	30.60	34.70	37.90	41.20	44.50	47.60	50.00
25	5.a	0.00	7.10	11.10	16.40	21.50	26.60	31.20	35.30	38.50	42.40	46.20	49.70	51.90
26	5.b	0.00	6.80	10.80	16.30	21.50	26.20	30.90	35.50	38.80	42.20	46.30	49.80	52.10
27	5.c	0.00	6.70	10.80	16.40	21.70	26.40	31.00	35.30	39.10	42.20	46.70	49.40	51.90
28	5.d	0.00	6.80	10.90	16.70	21.70	26.60	31.00	35.60	39.20	42.70	46.30	49.70	52.30

Response Data Reductions – Time Series (Disso) Data

Software automatically:

- handles test repeat data
- computes average profiles
- compute f1 & f2 curve fit metrics
- computes sensitive Weibull curve fit metrics
- computes additional profile response metrics
- Maps all computed responses to the experimental design for analysis



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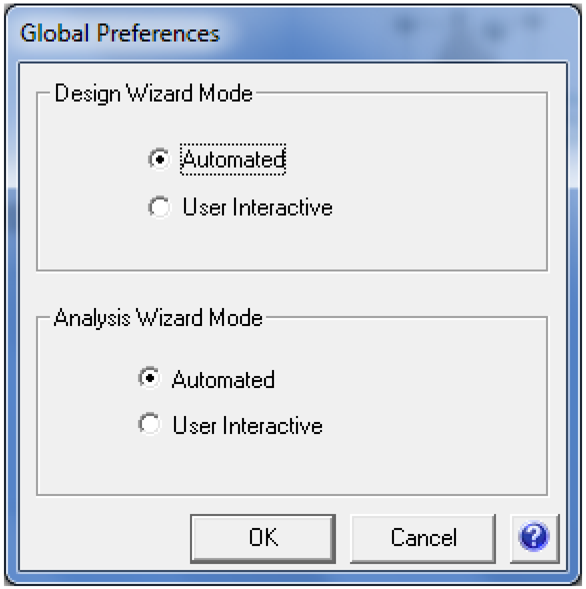
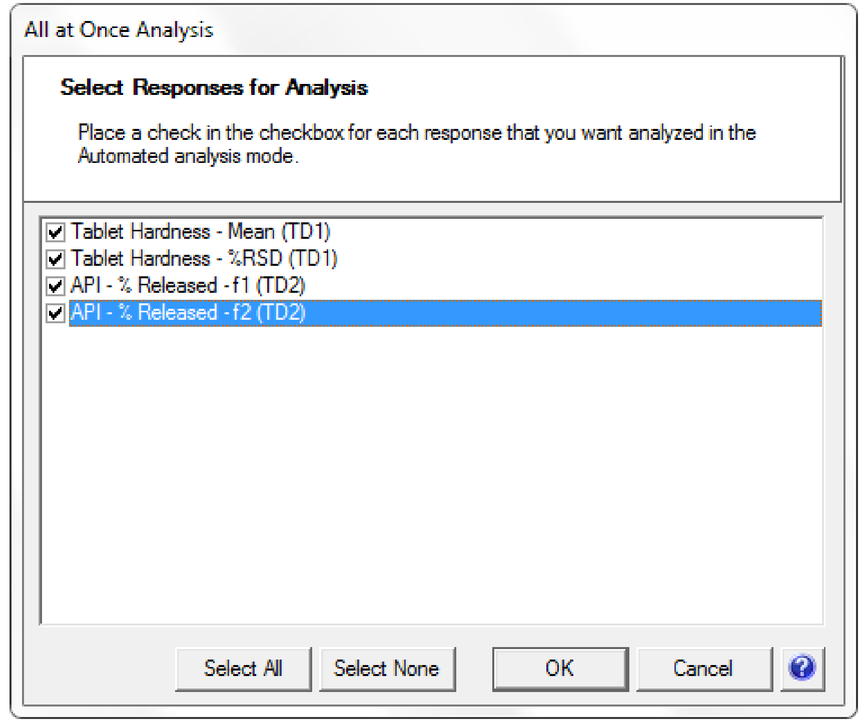
Response Data Reductions – Time Series (Disso) Data

	Run No.	Atomizing Air Pressure	Pattern Air Pressure	Spray Rate	Gun Distance	Tablet Hardness - Mean (TD1)	Tablet Hardness - %RSD (TD1)	API - % Released - f1	API - % Released - f2
1	1	30	55	82.5	7	75.18	1.47	4.34	77.81
2	2	30	27.5	82.5	10	75.07	0.61	22.12	48.22
3	3	50	0	125	10	77.15	1.01	43.07	34.01
4	4	10	0	40	10	76.23	1.53	6.68	71.35
5	5	10	55	125	10	75.65	0.80	9.43	64.77
6	6	10	55	40	4	75.76	0.71	34.35	38.90
7	7	30	27.5	82.5	4	74.24	1.44	22.50	47.91
8	8	30	0	82.5	7	75.91	1.82	4.47	77.43
9	9	50	55	40	10	74.63	1.66	8.02	68.57
10	10	50	0	40	4	75.52	1.07	3.25	83.71
11	11	30	27.5	82.5	7	74.52	1.29	9.56	64.14
12	12	10	55	40	10	74.62	0.97	1.49	94.63
13	13	10	0	125	4	74.38	0.76	14.47	56.86
14	14	50	55	40	4	75.89	1.71	14.61	56.70
15	15	10	0	40	4	75.43	2.35	13.35	58.25
16	16	10	0	125	10	77.25	1.54	28.74	43.14
17	17	50	55	125	10	75.54	0.89	28.92	43.02
18	18	50	27.5	82.5	7	74.68	1.34	8.82	65.99
19	19	50	0	40	10	76.06	1.42	20.05	50.01
20	20	30	27.5	82.5	7	74.77	1.61	8.82	65.99
21	21	10	55	125	4	74.76	0.91	36.56	37.62
22	22	50	55	125	4	74.81	1.52	13.37	58.29
23	23	10	0	40	4	75.43	0.77	11.75	60.52
24	24	10	27.5	82.5	7	74.68	1.02	9.43	64.46
25	25	30	27.5	82.5	7	74.70	0.93	9.30	64.78
26	26	30	27.5	40	7	74.70	1.15	5.17	75.79
27	27	10	55	40	4	75.94	1.52	34.67	38.73
28	28	50	0	125	4	74.39	1.69	3.64	82.18
29	29	50	0	40	4	75.46	1.43	3.45	82.83
30	30	30	27.5	125	7	74.59	1.58	14.15	57.25

Analysis Wizard. Automated Mode





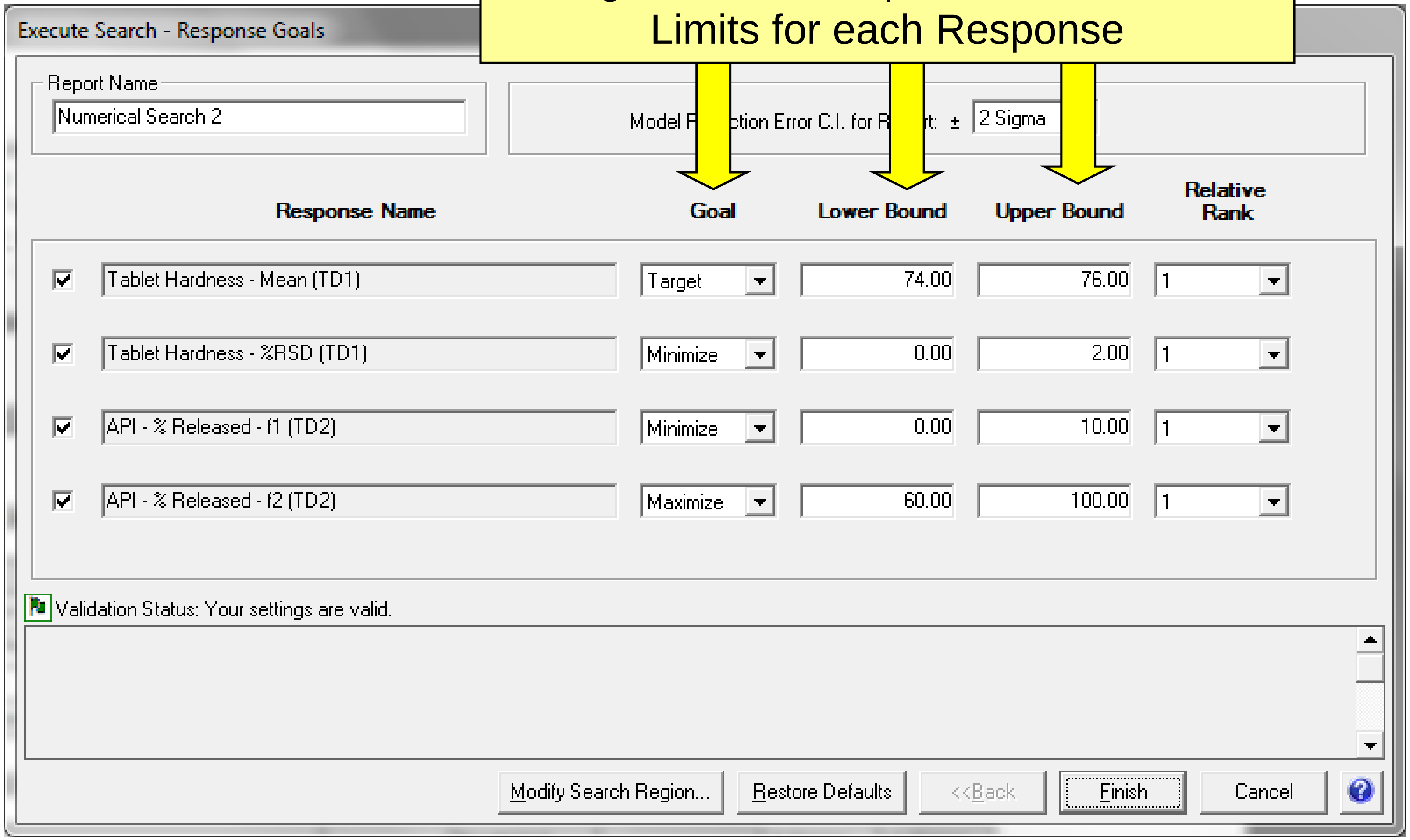
One Click:

Software automatically creates a predicitve and diagnostic equation (model) for each response that characterizes the effects of the study variables on the response.

S-Matrix®

Numerical Answer Search – Best Overall Conditions

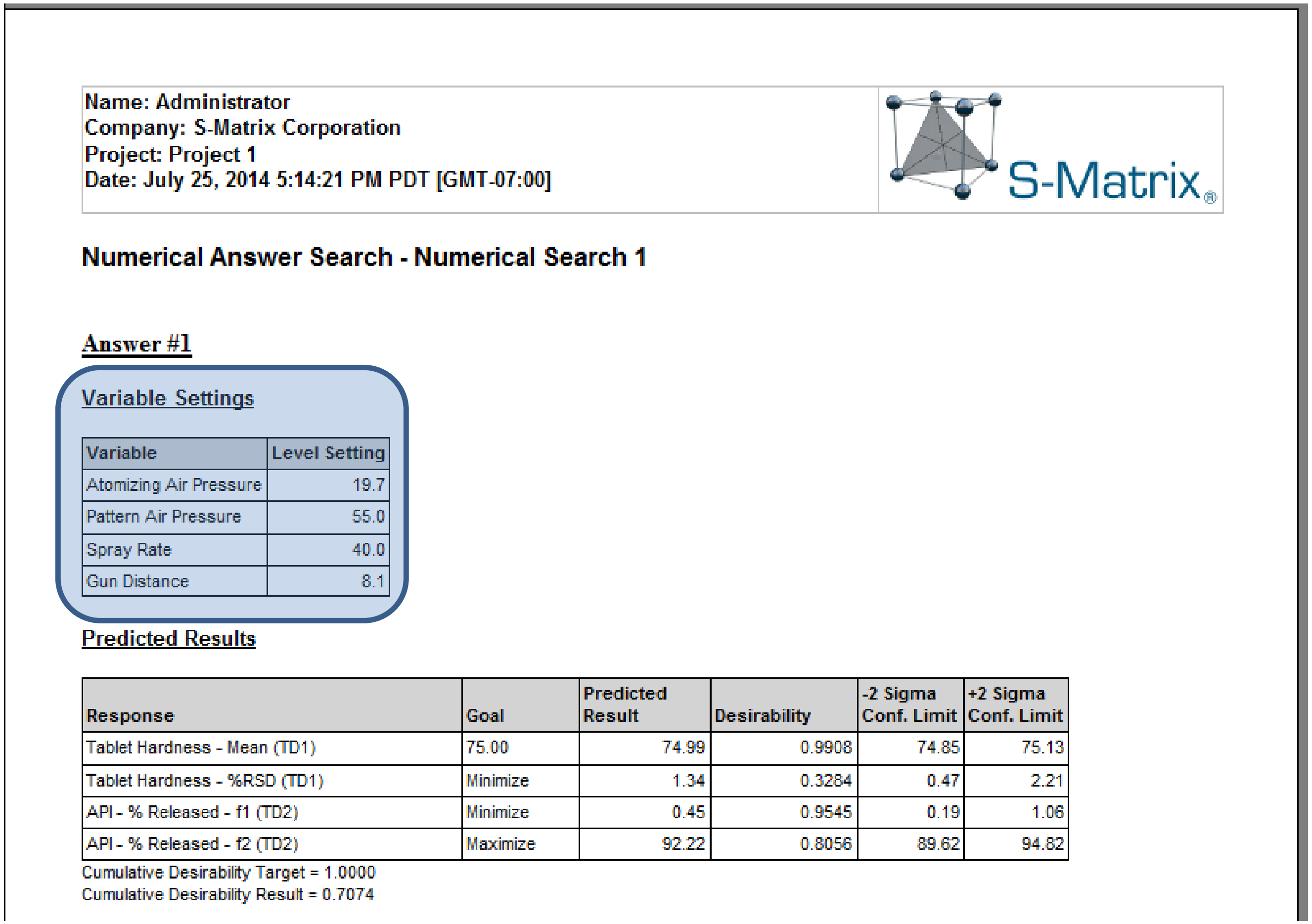
Set goals and Acceptable Performance Limits for each Response



S-Matrix®

Numerical Answer – Best Overall Conditions

The software automatically identifies and reports the best overall answer – the level setting combination which meets your defined performance goals for all responses simultaneously.



Name: Administrator
Company: S-Matrix Corporation
Project: Project 1
Date: July 25, 2014 5:14:21 PM PDT [GMT-07:00]

Numerical Answer Search - Numerical Search 1

Answer #1

Variable Settings

Variable	Level Setting
Atomizing Air Pressure	19.7
Pattern Air Pressure	55.0
Spray Rate	40.0
Gun Distance	8.1

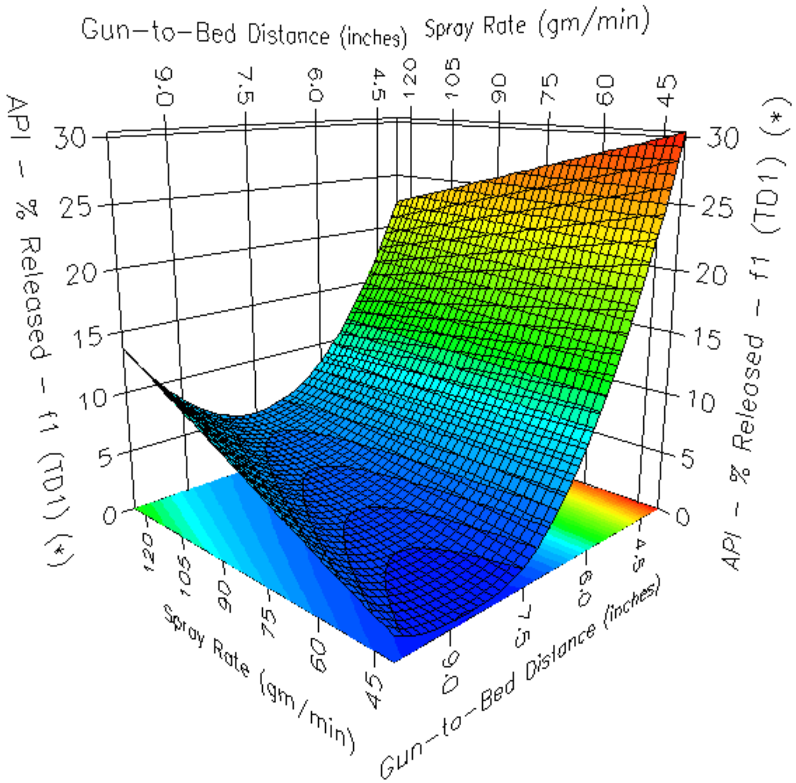
Predicted Results

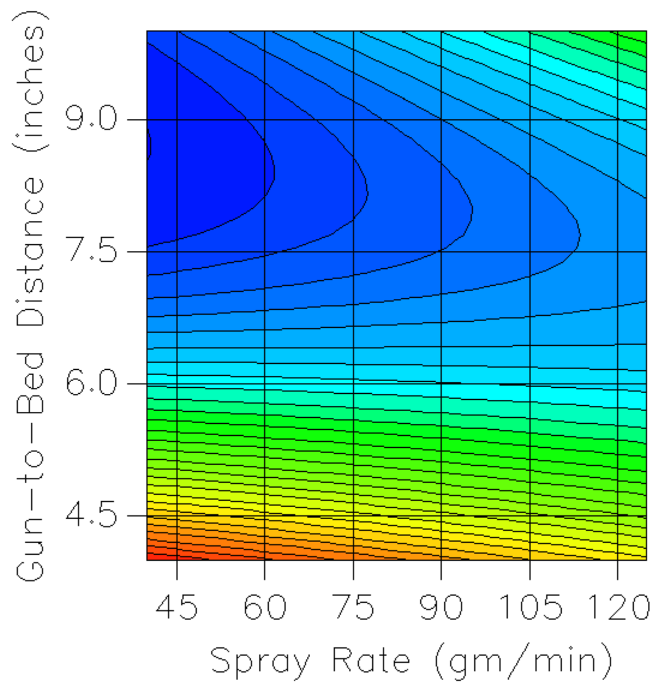
Response	Goal	Predicted Result	Desirability	-2 Sigma Conf. Limit	+2 Sigma Conf. Limit
Tablet Hardness - Mean (TD1)	75.00	74.99	0.9908	74.85	75.13
Tablet Hardness - %RSD (TD1)	Minimize	1.34	0.3284	0.47	2.21
API - % Released - f1 (TD2)	Minimize	0.45	0.9545	0.19	1.06
API - % Released - f2 (TD2)	Maximize	92.22	0.8056	89.62	94.82

Cumulative Desirability Target = 1.0000
Cumulative Desirability Result = 0.7074

Graphical Visualization – Best Overall Conditions

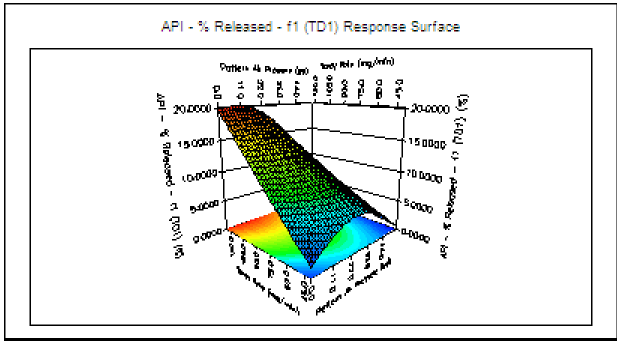
The graphics wizards can generate graphical representations which visualize the linear, interaction, and complex effects of the study variables for each critical response.

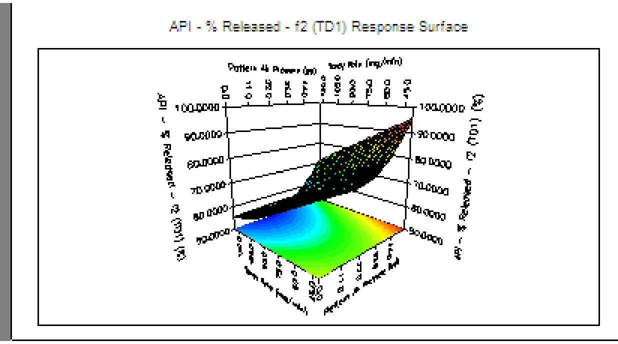


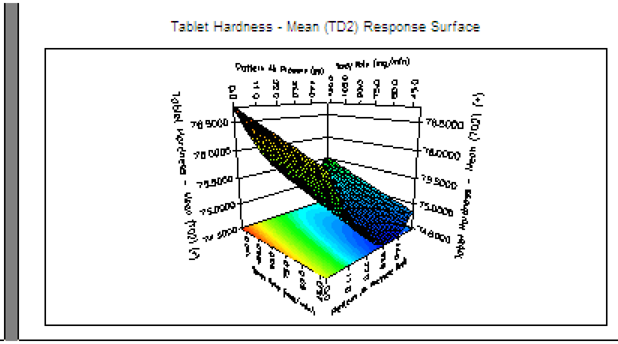


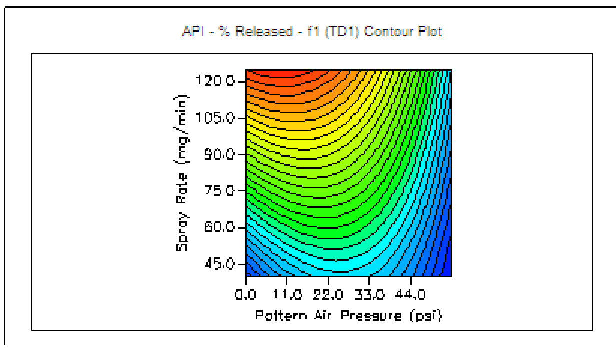
Graphical Visualization – Best Overall Conditions

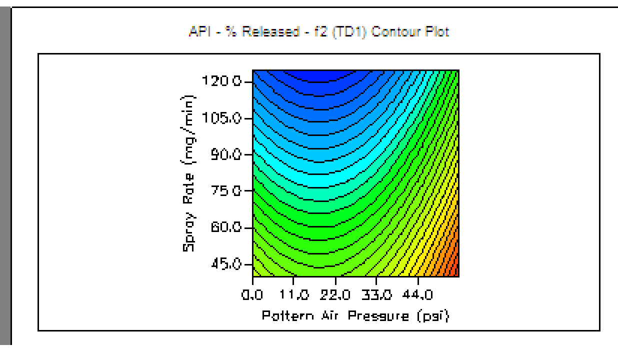
Note: different Critical Quality Attributes have different regions of good performance.

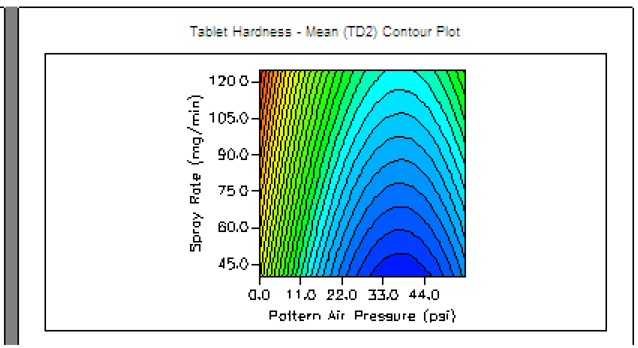












X- Axis = Pattern Air Pressure (psi)
Y-Axis = Spray Rate (mg/min)

Atomizing Air Pressure = 10 psi
Gun-to-Bed Distance = 9 inches

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Graphical Visualization – Mean Performance Design Space

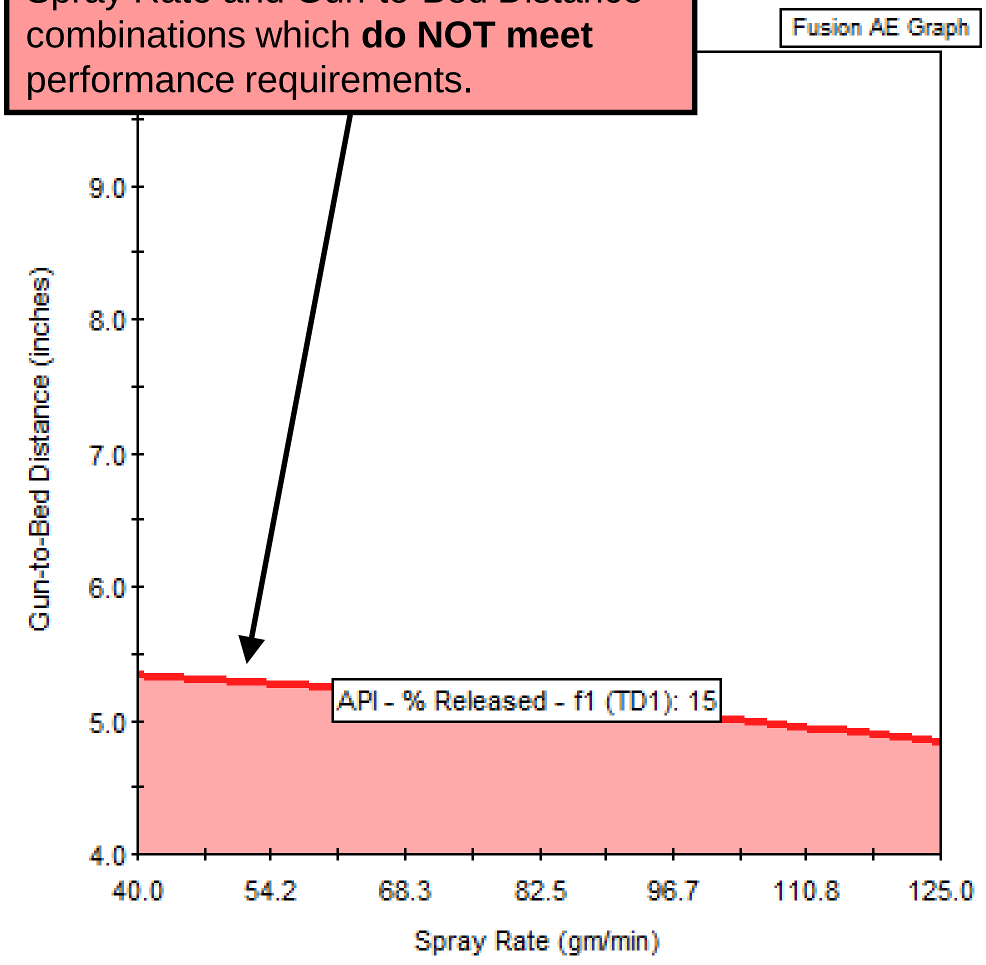
Fusion Pro Overlay Graph.

Each color on the graph corresponds to a response for which goals have been defined.

A region shaded with a given color shows the study variable level setting combinations that will NOT meet the goals for the corresponding response.

Note: the un-shaded region corresponds to level setting combinations that meet all response goals.

Note: Shaded region indicates the Spray Rate and Gun-to-Bed Distance combinations which **do NOT meet** performance requirements.



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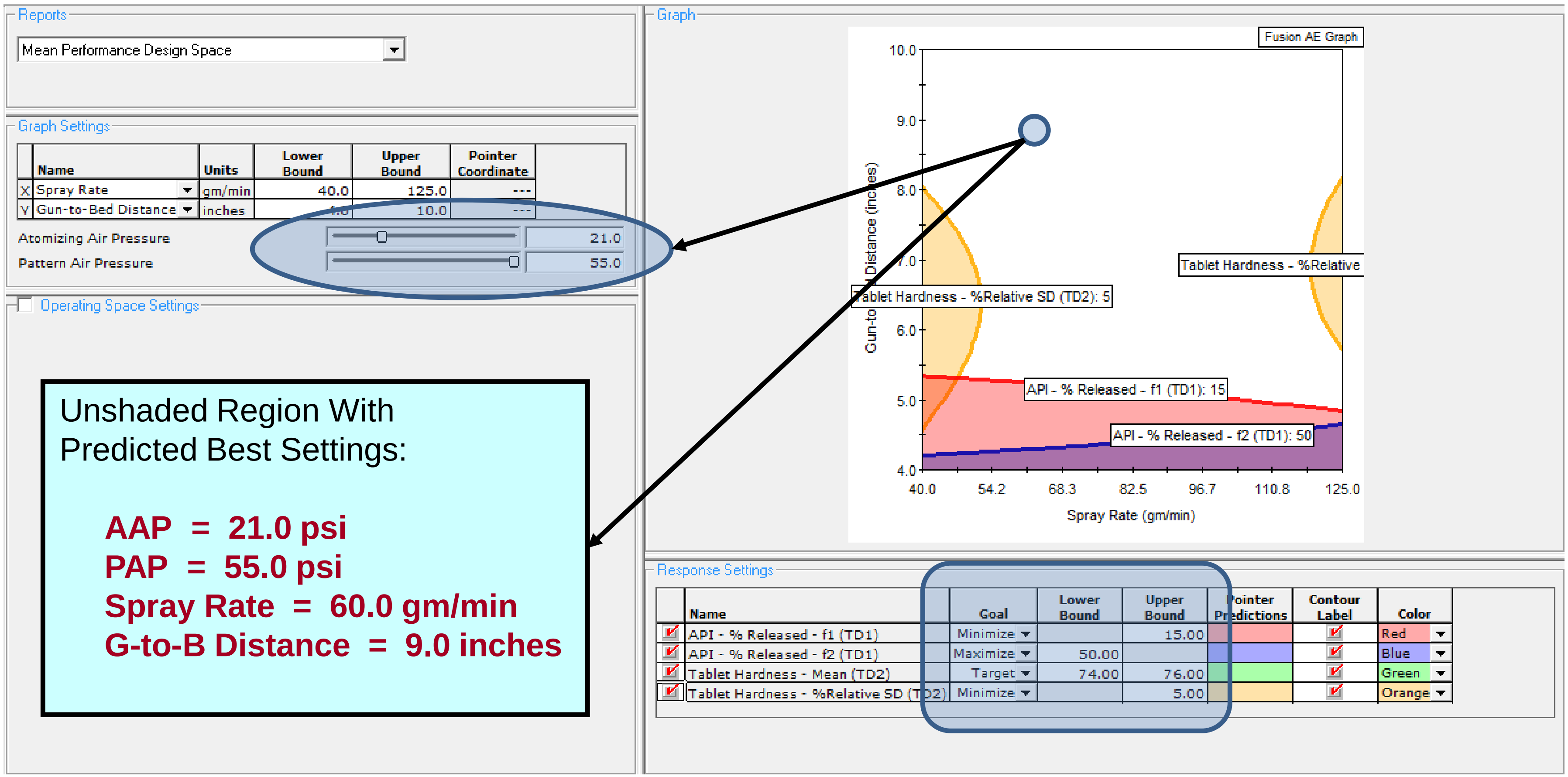
Graphical Visualization – Mean Performance Design Space



Unshaded Region With
Predicted Best Settings:

AAP = 21.0 psi
PAP = 55.0 psi
Spray Rate = 60.0 gm/min
G-to-B Distance = 9.0 inches

S-Matrix®

Graphical Visualization – Mean Performance Design Space

Mean Performance Edges of Failure

Reports

Mean Performance Design Space

Graph Settings

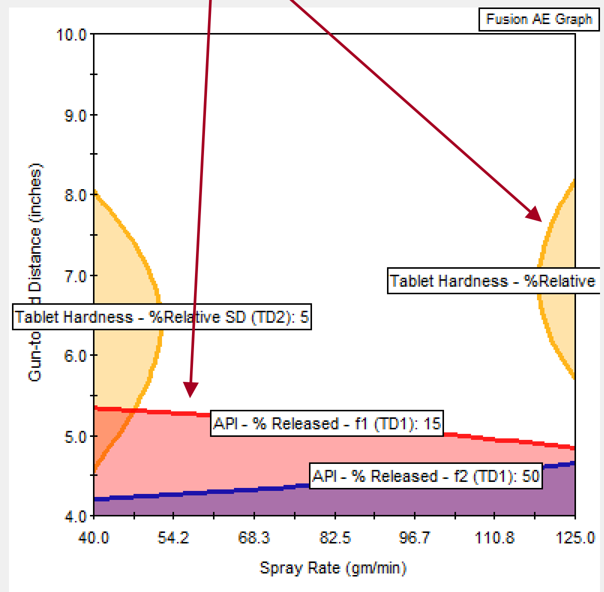
	Name	Units	Lower Bound	Upper Bound	Pointer Coordinate
X	Spray Rate	gm/min	40.0	125.0	---
Y	Gun-to-Bed Distance	inches	4.0	10.0	---

Atomizing Air Pressure 21.0

Pattern Air Pressure 55.0

Operating Space Settings

Graph



Response Settings

	Name	Goal	Lower Bound	Upper Bound	Pointer Predictions	Contour Label	Color
☑	API - % Released - f1 (TD1)	Minimize		15.00		☑	Red
☑	API - % Released - f2 (TD1)	Maximize	50.00			☑	Blue
☑	Tablet Hardness - Mean (TD2)	Target	74.00	76.00		☑	Green
☑	Tablet Hardness - %Relative SD (TD2)	Minimize		5.00		☑	Orange

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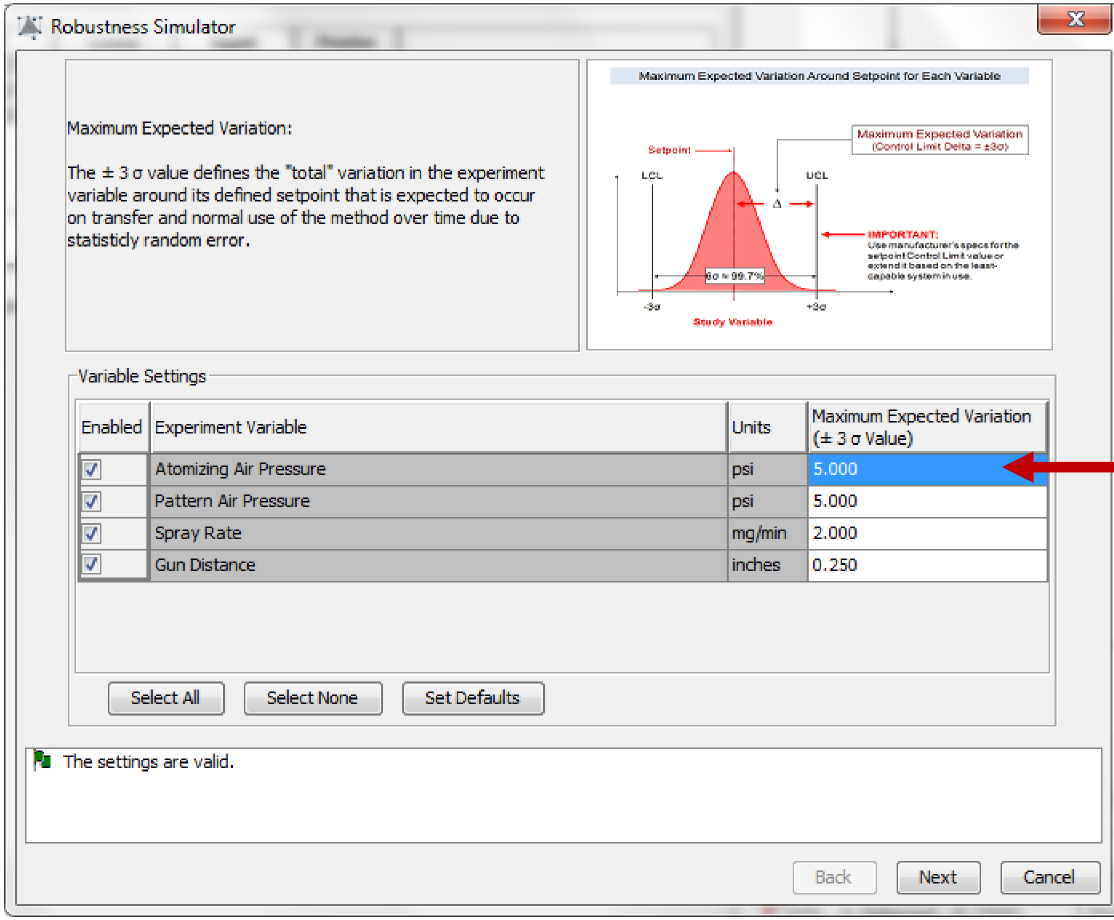
Robustness Simulation – Expected Variation of CPPs



NOTE - the value defines the maximum expected setpoint variation for the study factor.

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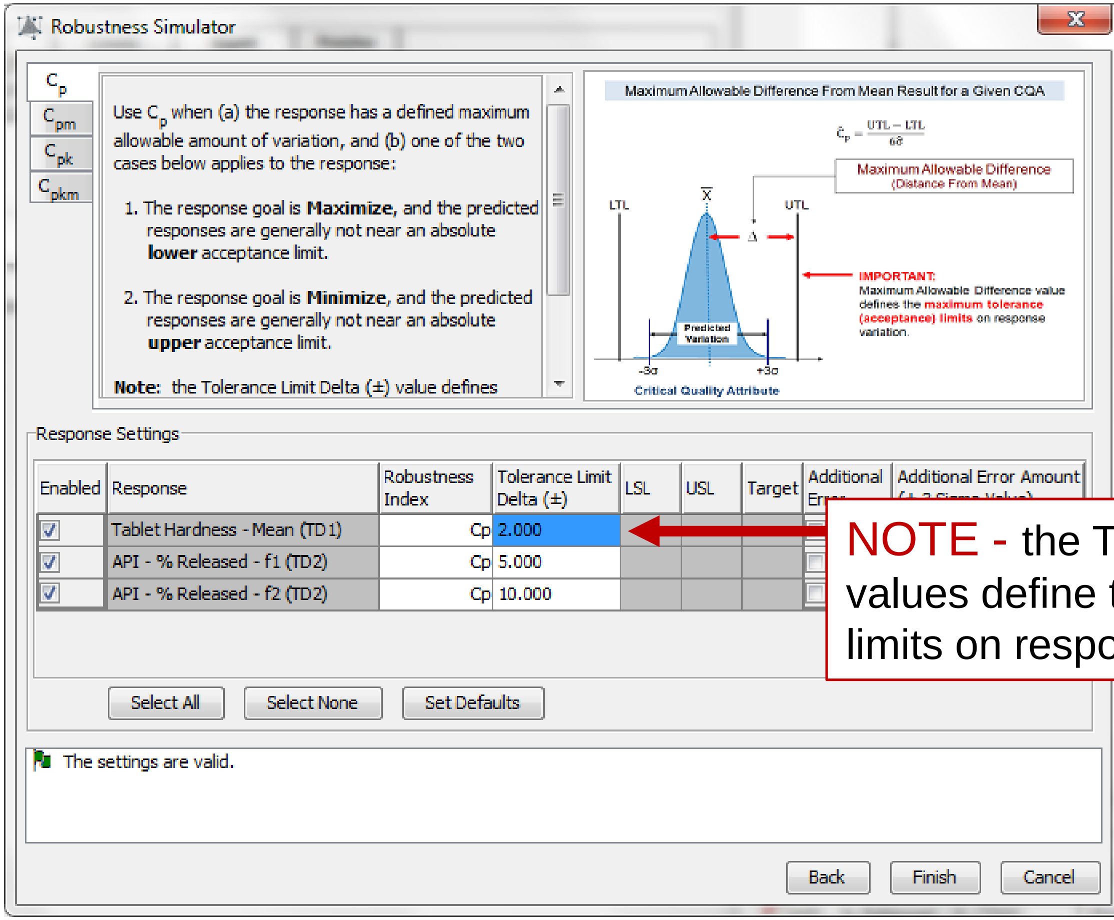
Robustness Simulation – Acceptable Variation Limits in CQAs



NOTE - the Tolerance Limit Delta values define the maximum allowable ± limits on response variation.

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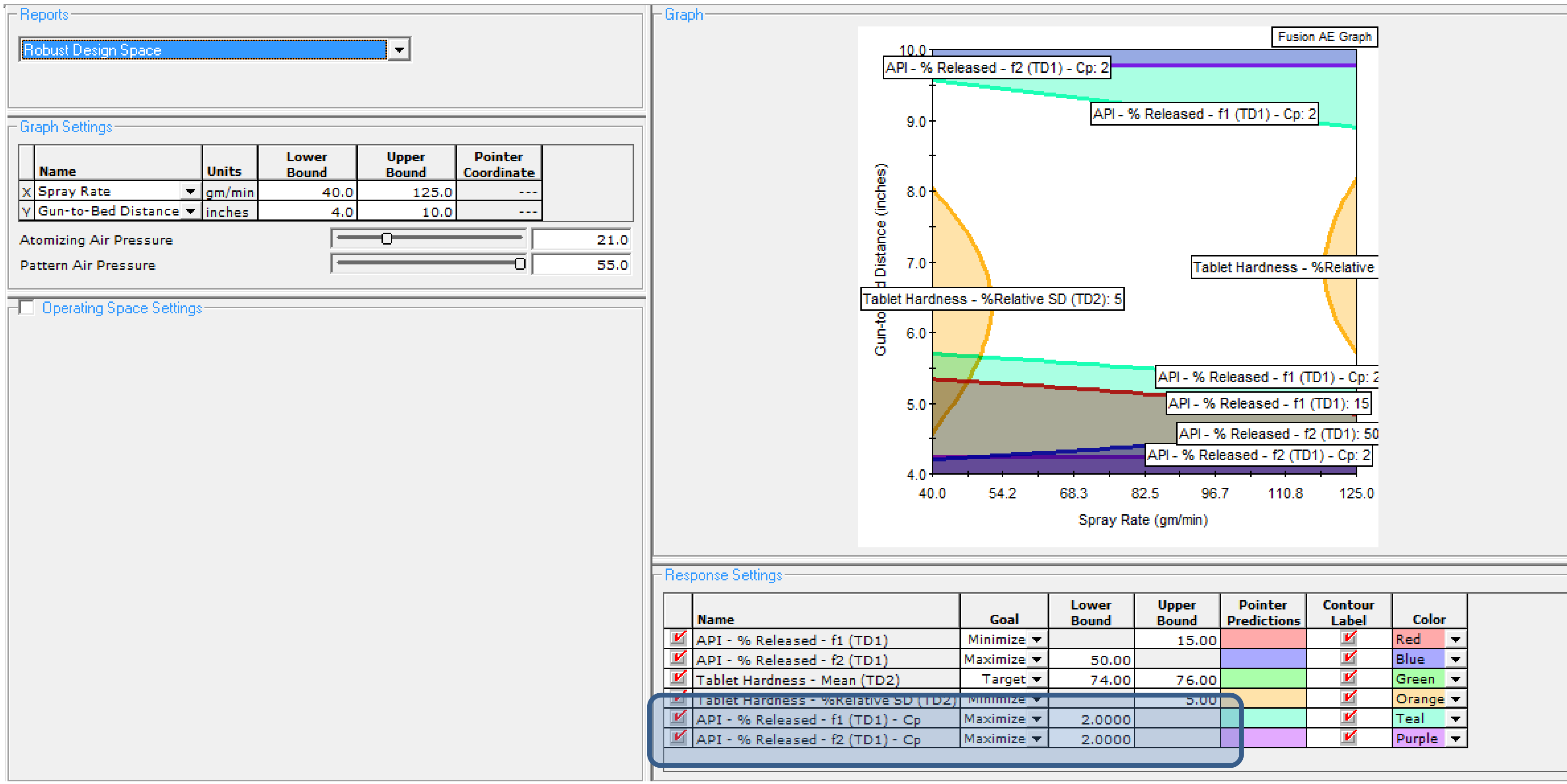
Final Design and Operating Space – Mean Performance + Robustness

The software automatically visualizes the final robust design space.



S-Matrix®

Final Design and Operating Space – Mean Performance + Robustness

You can also graphically represent your safe operating ranges within the region, and the software will define verification runs to demonstrate that all performance goals are met.

Reports

Robust Design Space

Graph Settings

	Name	Units	Lower Bound	Upper Bound	Pointer Coordinate
X	Spray Rate	gm/min	40.0	125.0	
Y	Gun-to-Bed Distance	inches	4.0	10.0	

Atomizing Air Pressure 21.0

Pattern Air Pressure 55.0

Operating Space Settings

Operating Ranges

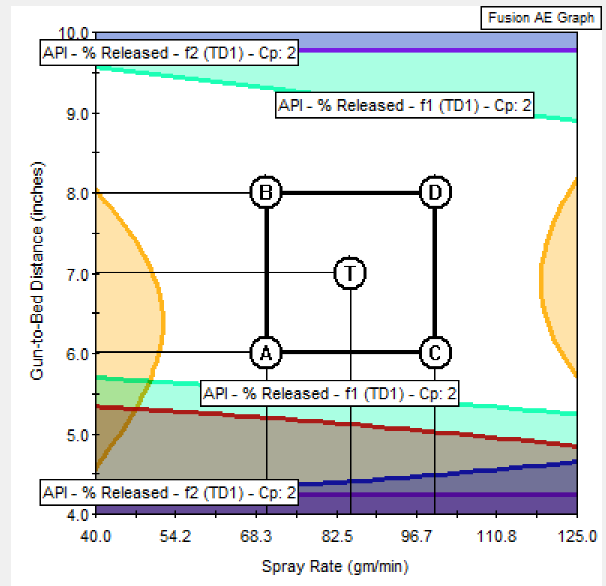
Variable	Lower Bound	Upper Bound	Center Point
Spray Rate	70.0	100.0	85.0
Gun-to-Bed Distance	6.0	8.0	7.0

Verification Runs

Show Verification Run Labels

	Point	Run ID	Atomizing Air Pressure	Pattern Air Pressure	Spray Rate	Gun-to-Bed Distance
1	A	Robust_Desig	21.0	55.0	70.0	6.0
2	B	Robust_Desig	21.0	55.0	70.0	8.0
3	C	Robust_Desig	21.0	55.0	100.0	6.0
4	D	Robust_Desig	21.0	55.0	100.0	8.0
5	T	Robust_Desig	21.0	55.0	85.0	7.0

Graph



Response Settings

Name	Goal	Lower Bound	Upper Bound	Target Predictions	Pointer Predictions	Contour Label	Color
API - % Released - f1 (TD1)	Minimize		15.00	4.51			Red
API - % Released - f2 (TD1)	Maximize	50.00		76.73			Blue
Tablet Hardness - Mean (TD2)	Target	74.00	76.00	75.22			Green
Tablet Hardness - %Relative SD (TD2)	Minimize		5.00	2.39			Orange
API - % Released - f1 (TD1) - Cp	Maximize	2.0000		3.4708		✓	Teal
API - % Released - f2 (TD1) - Cp	Maximize	2.0000		5.1526		✓	Purple

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Fusion Pro – QbD-aligned R&D Software

Case Study 1 – END

Fusion Pro – QbD-aligned R&D Software

Case Study 2 –

Tablet Excipient
Formulation & Processing

Case Study 2 –Tablet Excipient Study

The three critical excipient formulation parameters (CPPs) selected for study are entered into the Experiment Setup template shown below.

The one critical excipient process parameter (CPPs) selected for study is also entered into the Experiment Setup template shown below.

Mixture Variable Settings

No. of Mixture Variables: 3

Units: %

Mixture Amount: 100.0

Mixture Variable	State	Lower Bound	Upper Bound
Excipient 1	Variable	0.0	100.0
Excipient 2	Variable	0.0	100.0
Excipient 3	Variable	0.0	100.0

Process Variable Settings

No. of Process Variables: 1

Name	Units	Type	Lower Bound	Upper Bound
Compaction Force	kN	Continuous	10.0	21.0

State

- (•) Variable
- ( ) Constant

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Case Study 2 –Tablet Excipient Study

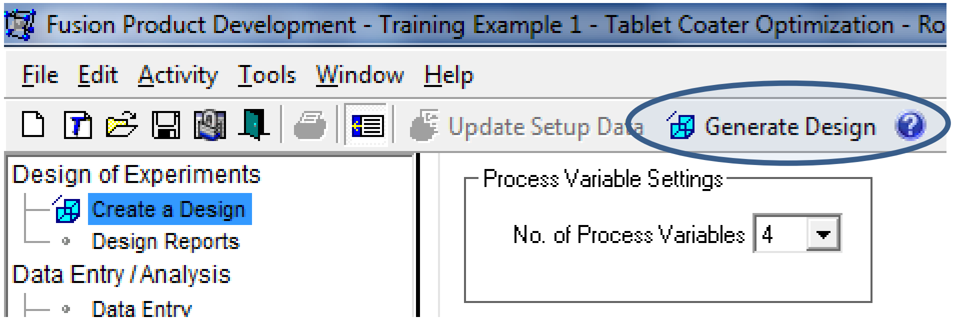
The experiment was undertaken to optimize the excipient formulation and the critical process parameter for two critical tablet quality attributes:

Friability and Dissolution Profile

For the dissolution response, the two critical release goals were:

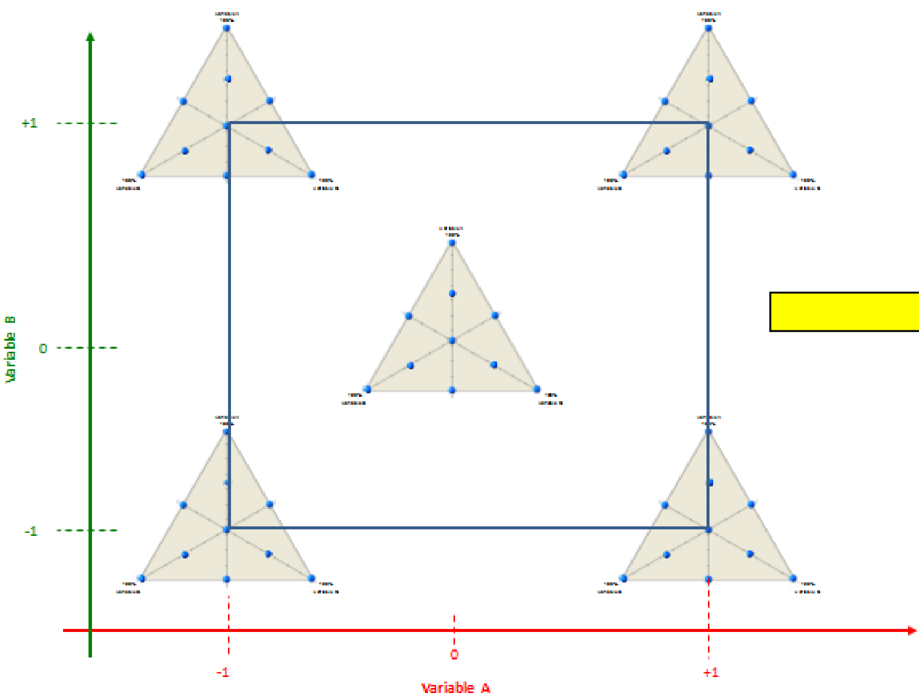
- 10% Released at t = 10 minutes
- 25% Released at t = 60 minutes.

Automated Experiment Design Generation



One Click:

Software maps the experimental design to the study factors.



Run No.	Excipient 1	Excipient 2	Excipient 3	Compaction Force
1	0	0	100	15.12
2	50	0	50	15.12
3	100	0	0	20.35
4	0	100	0	9.88
5	0	50	50	20.35
6	16.7	66.7	16.6	17.73
7	0	100	0	15.12
8	100	0	0	15.12
9	0	50	50	9.88
10	0	0	100	9.88
11	50	0	50	20.35
12	0	0	100	20.35
13	50	50	0	15.12
14	100	0	0	9.88
15	66.7	16.7	16.6	12.5
16	16.7	16.7	66.6	17.73
17	0	100	0	9.88
18	50	50	0	20.35
19	0	0	100	20.35
20	33.3	33.3	33.4	15.12
21	0	100	0	20.35
22	66.7	16.7	16.6	17.73
23	0	100	0	20.35
24	33.3	33.3	33.4	15.12
25	50	50	0	9.88
26	16.7	66.7	16.6	12.5
27	0	0	100	9.88
28	50	0	50	9.88
29	16.7	16.7	66.6	12.5

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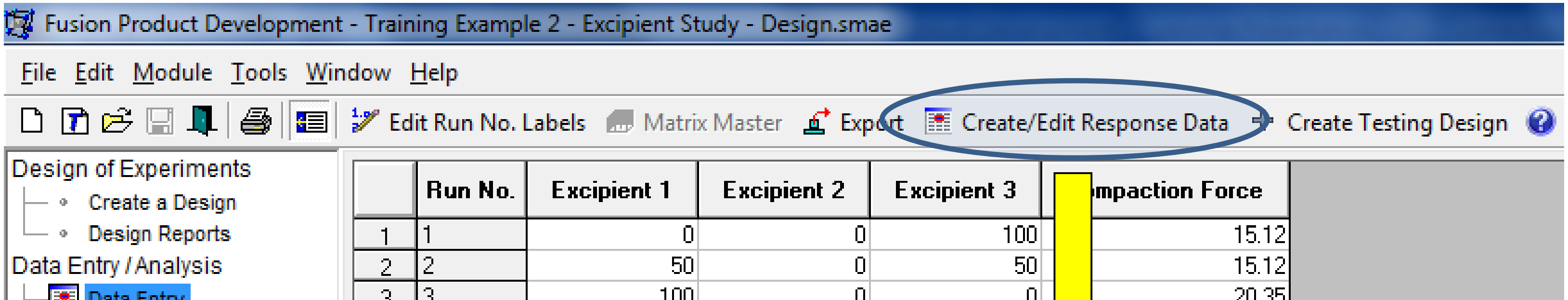
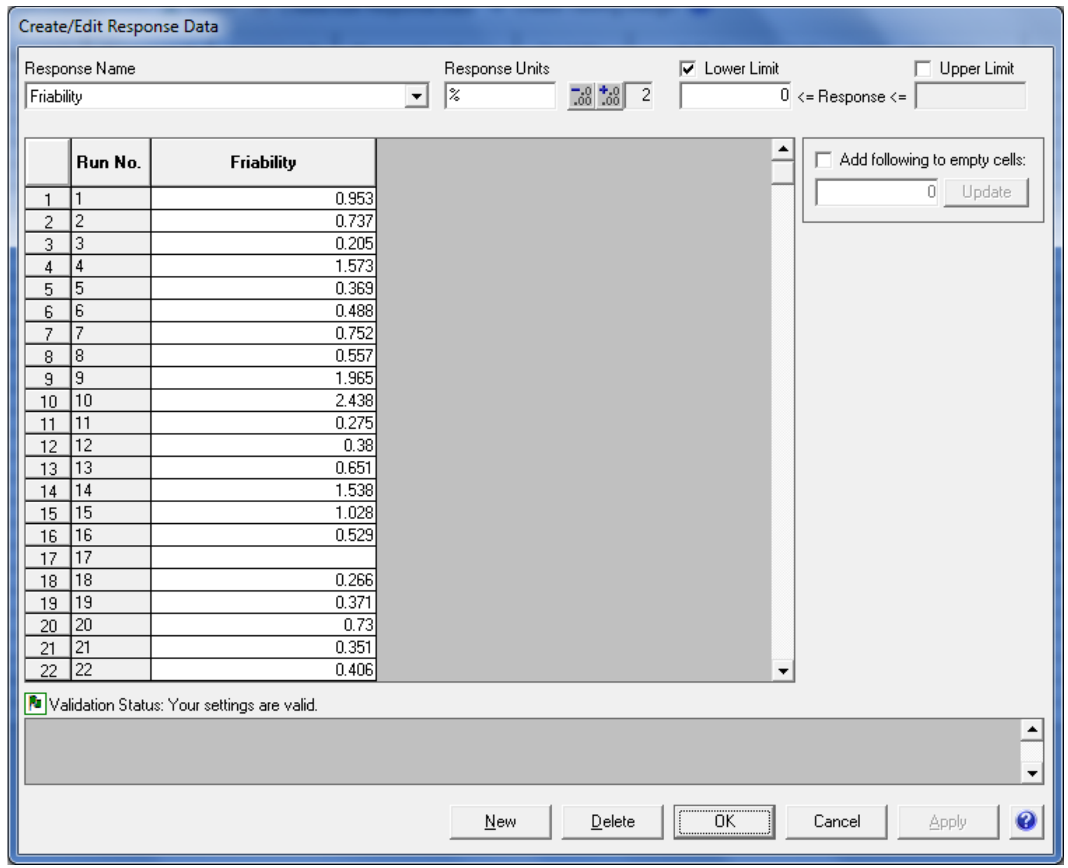
Enter Test Results – Friability Testing

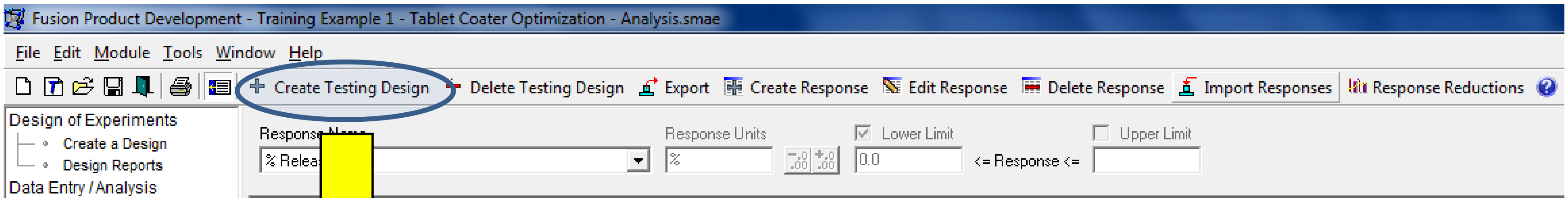


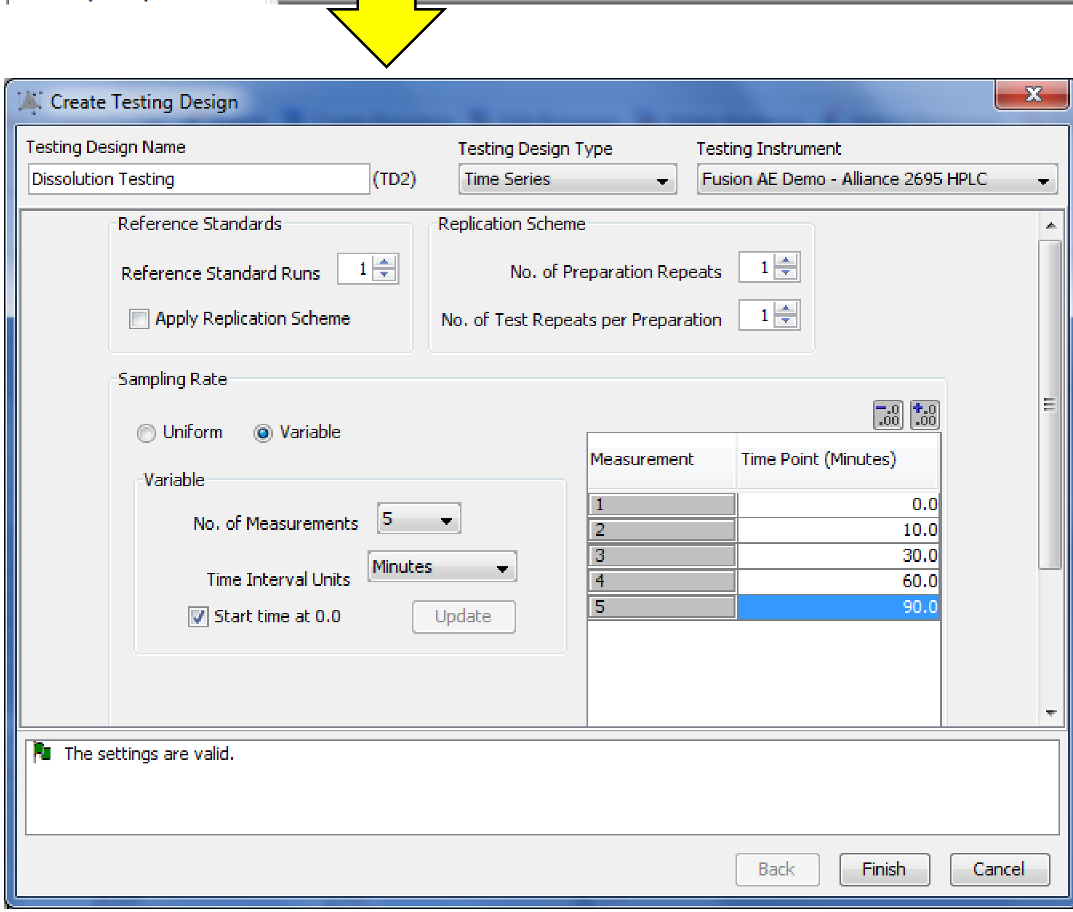
Responses consisting of only one measurement per run (no test repeats) can be entered directly onto the Experiment Design grid.



S-Matrix®

Create Testing Design – Time Series (Dissolution) Testing



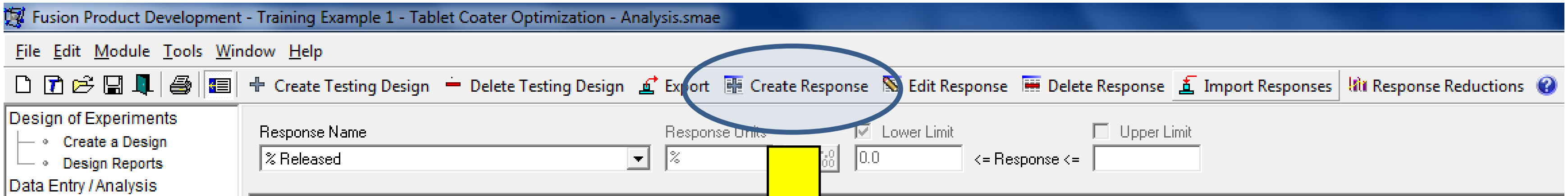


Software automatically handles:

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

S-Matrix®

Create Testing Design – Enter Test Results



	A Run No.	B t - 10.00	C t - 60.00
1	1	78.18	99.17
2	2	11.18	19.40
3	3	8.56	20.87
4	4	4.64	24.91
5	5	21.56	36.29
6	6	6.33	21.63
7	7	5.95	25.50
8	8	8.49	20.24
9	9	13.72	35.71
10	10	78.07	99.01
11	11	11.14	20.10
12	12	78.10	99.26
13	13	4.84	18.64
14	14	8.45	20.51
15	15	8.48	17.68
16	16	10.70	26.66
17	17		
18	18	5.41	17.70
19	19	77.89	99.82
20	20	6.79	21.18
21	21	8.03	26.06
22	22	9.10	19.24
23	23	8.12	25.65
24	24	6.71	20.97
25	25	4.23	18.08
26	26	5.14	22.31
27	27	78.24	98.75
28	28	11.14	18.89
29	29	10.07	26.79

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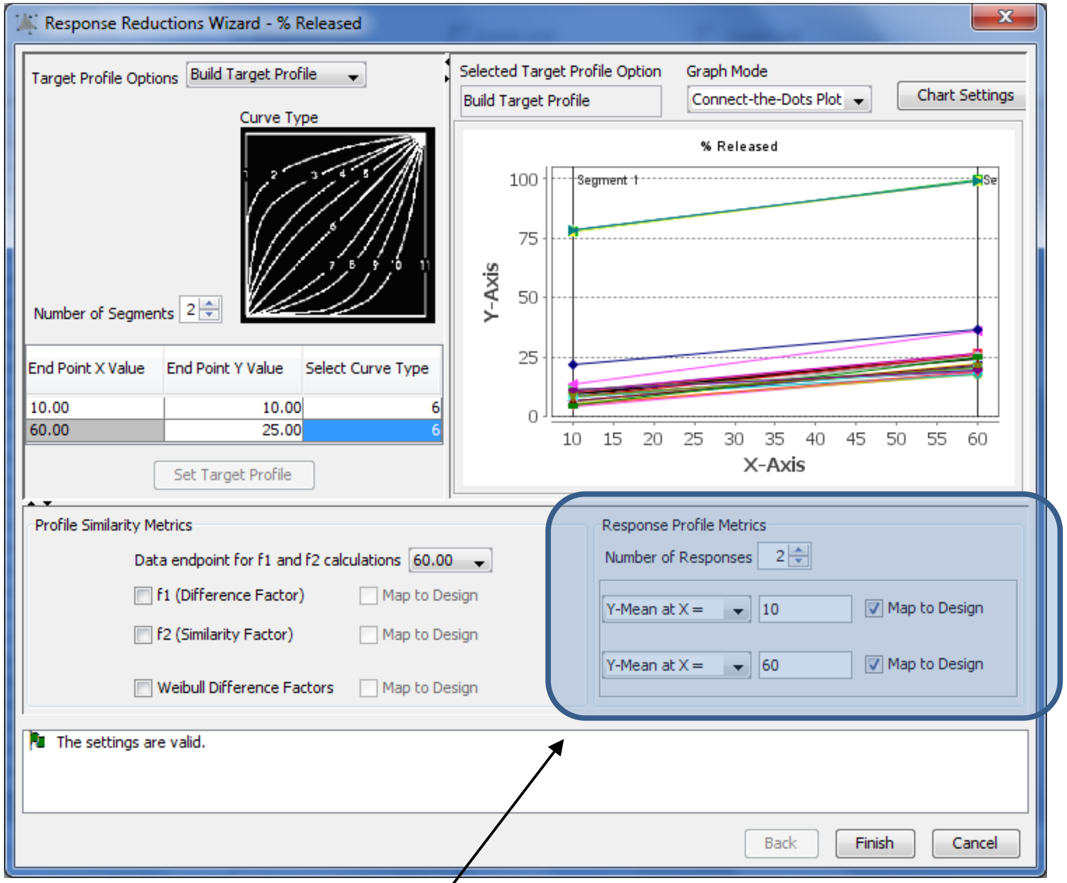
Response Data Reductions – Time Series (Disso) Data

Software automatically:

- handles test repeat data
- computes average profiles
- compute f1 & f2 curve fit metrics
- computes sensitive Weibull curve fit metrics
- computes additional profile response metrics
- Maps all computed responses to the experimental design for analysis



Two critical release goals:

- % Released at t = 10 minutes
- % Released at t = 60 minutes.

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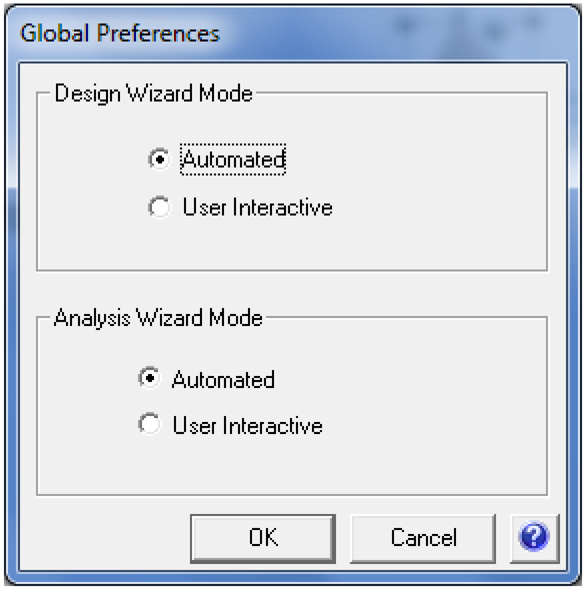
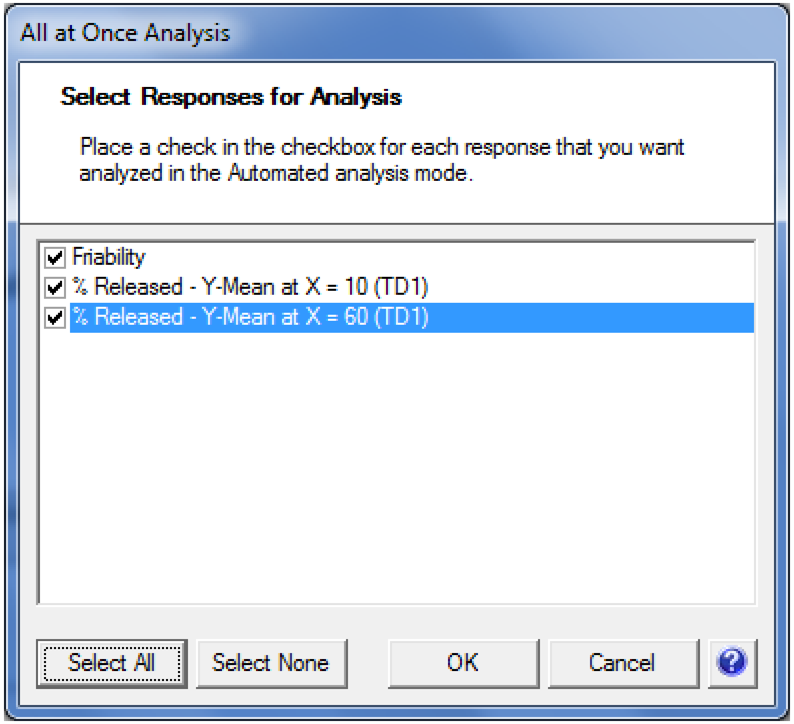
Analysis Wizard. Automated Mode





One Click:

Software automatically creates a predicitve and diagnostic equation (model) for each response that characterizes the effects of the study variables on the response.

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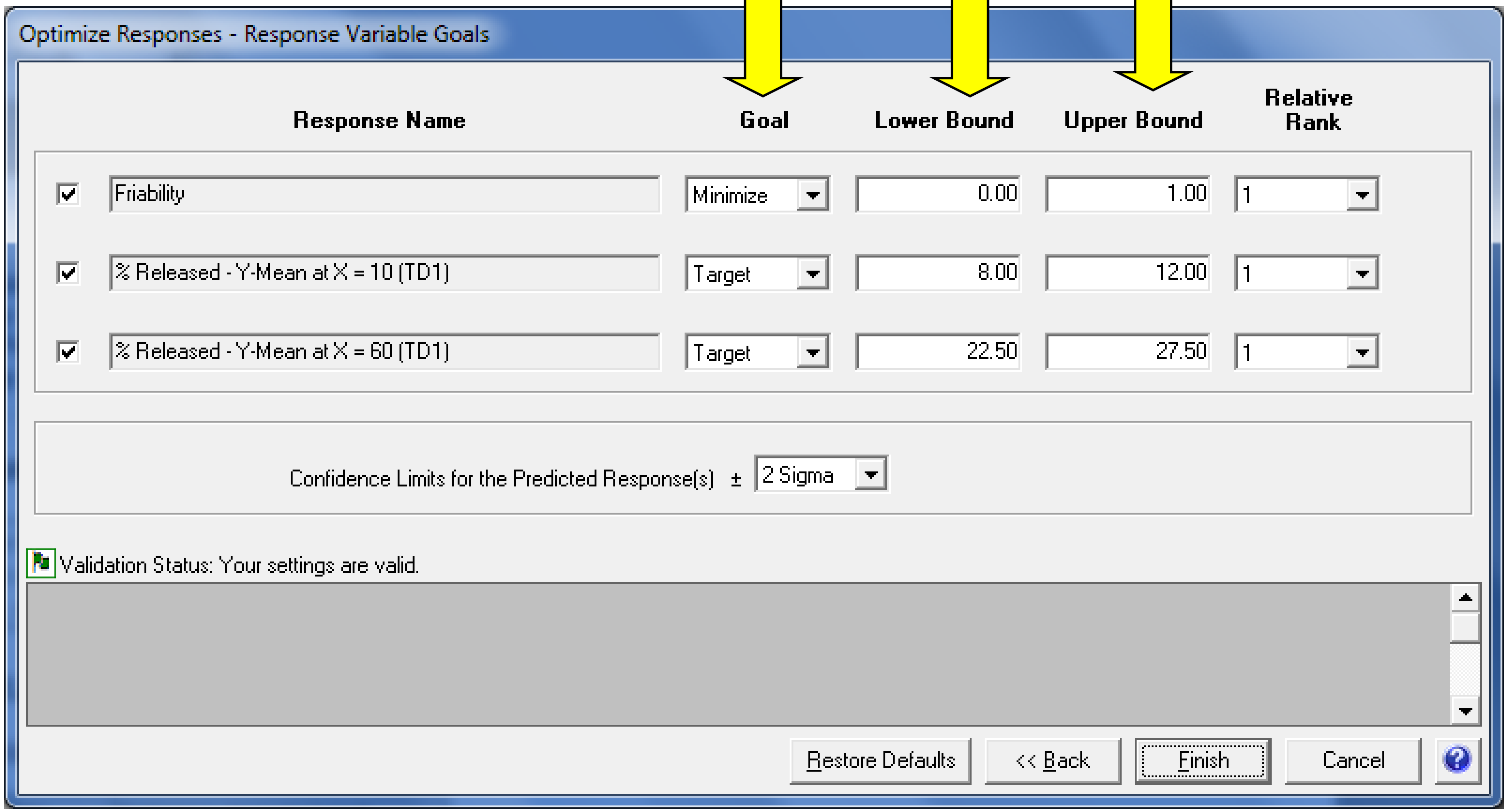
Numerical Answer Search – Best Overall Conditions

Set goals and Acceptable Performance Limits for each Response



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Numerical Answer – Best Overall Conditions

The software automatically identifies and reports the best overall answer – the level setting combination which meets your defined performance goals for all responses simultaneously.

Name: Administrator
Company: S-Matrix Corporation
Project: Project 1
Date: November 4, 2012 7:31:42 PM PST [GMT-08:00]

S-Matrix®

Numerical Search Results - Excipient Formulation Study

Answer #1

Variable Settings

Variable	Level Setting
Excipient 1	19.879929450
Excipient 2	18.897547896
Excipient 3	61.222522654
Compaction Force	20.35

Predicted Results

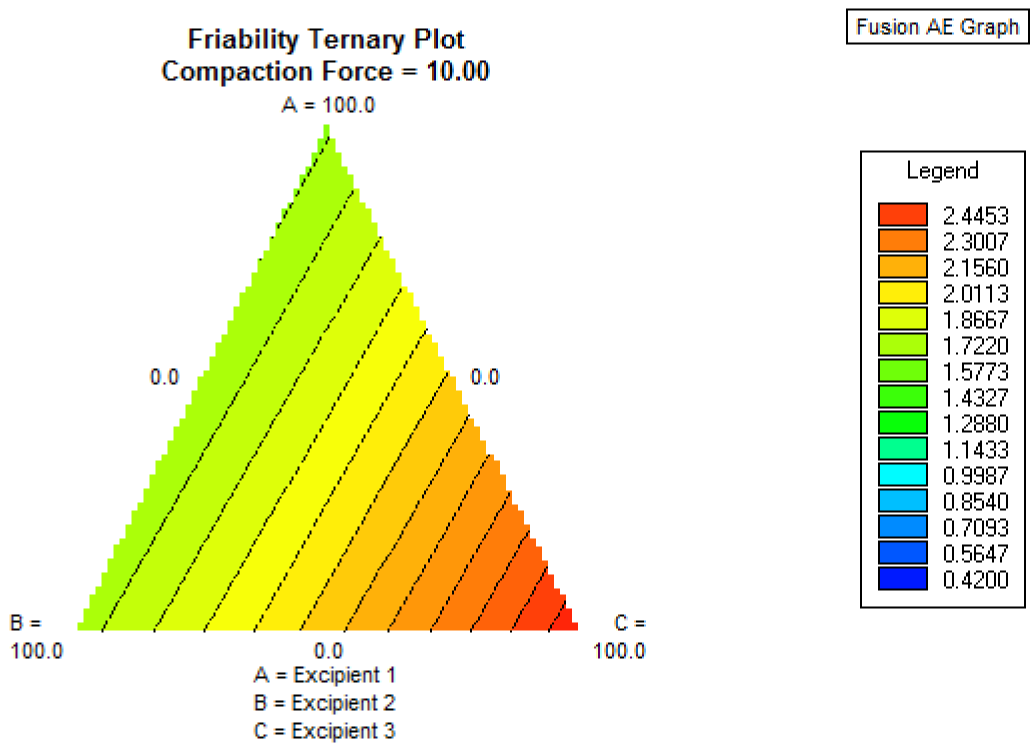
Response	Goal	Predicted Result	Desirability	-2 Sigma Conf. Limit	+2 Sigma Conf. Limit
Friability	Minimize	0.33	0.6719	0.32	0.34
% Released - Y-Mean at X = 10 (TD1)	10.0	10.00	1.0000	9.39	10.65
% Released - Y-Mean at X = 60 (TD1)	25.0	25.00	1.0000	23.60	26.53

Cumulative Desirability Target = 1.0000
Cumulative Desirability Result = 0.8759

S-Matrix®

Graphical Visualization – Best Overall Conditions

The graphics wizards can generate graphical representations which visualize the linear, interaction, and complex effects of the study variables for each critical response.



S-Matrix®

Graphical Visualization – Mean Performance Design Space

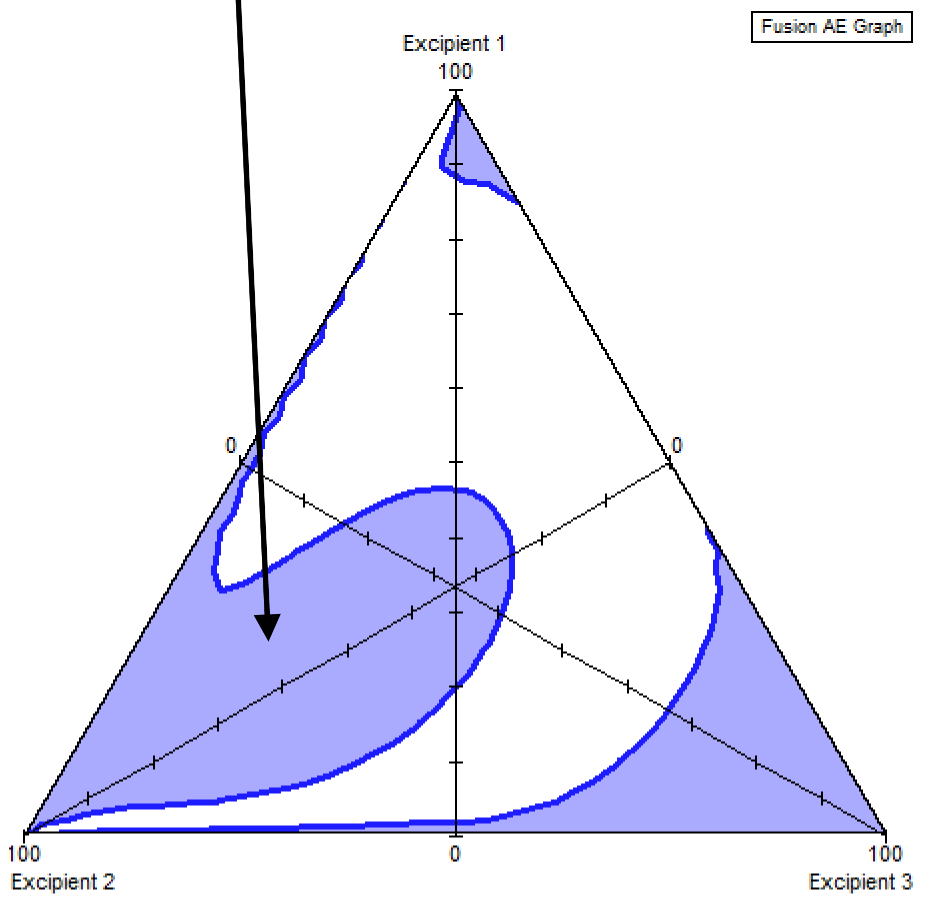
Fusion Pro Overlay Graph.

Each color on the graph corresponds to a response for which goals have been defined.

A region shaded with a given color shows the study variable level setting combinations that will NOT meet the goals for the corresponding response.

Note: the un-shaded region corresponds to level setting combinations that meet all response goals.

Note: Shaded region in this graph identifies all excipient formulations which **do NOT meet** performance requirements for % Released at 10 Minutes.



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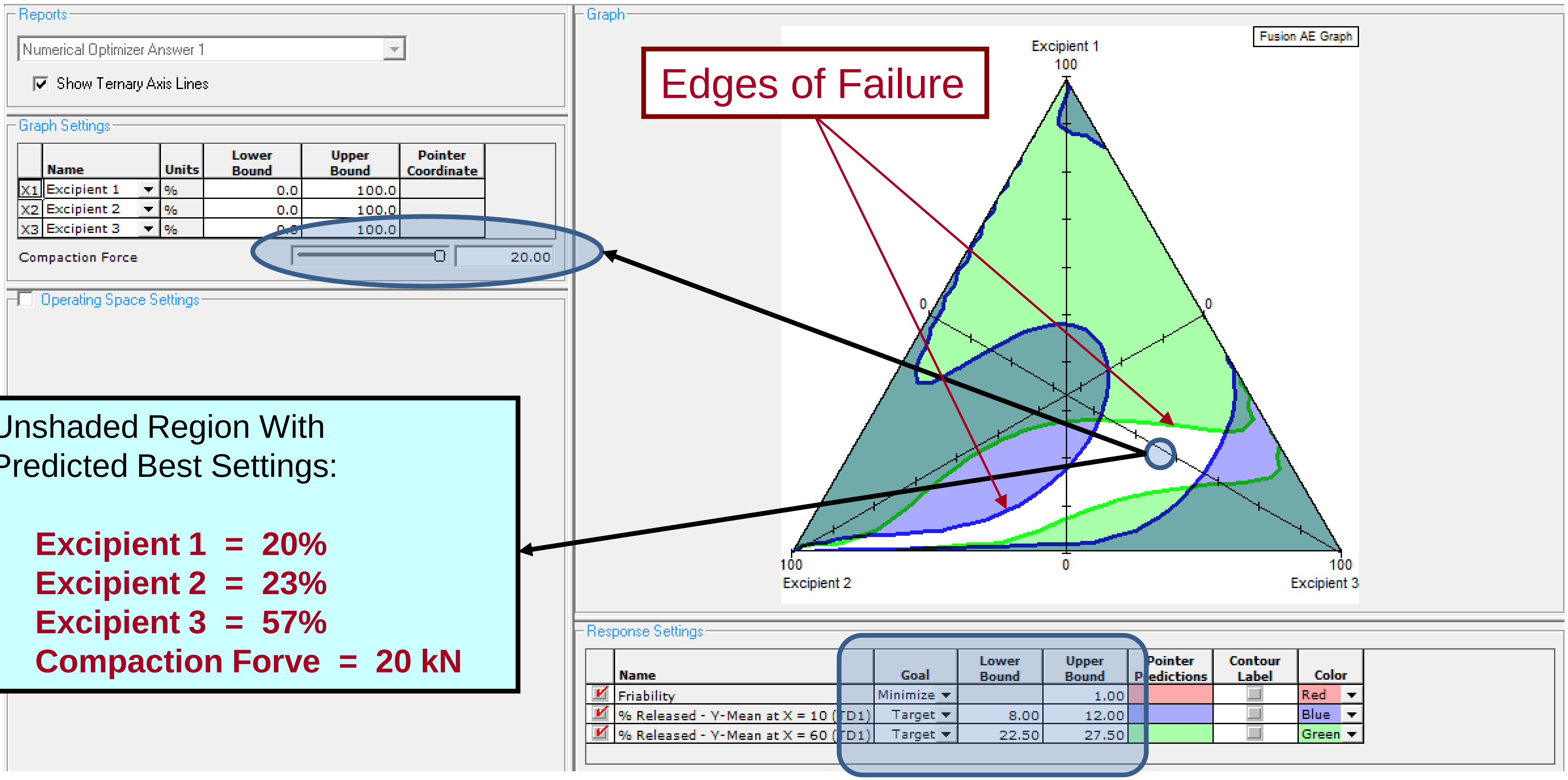
Graphical Visualization – Mean Performance Design Space

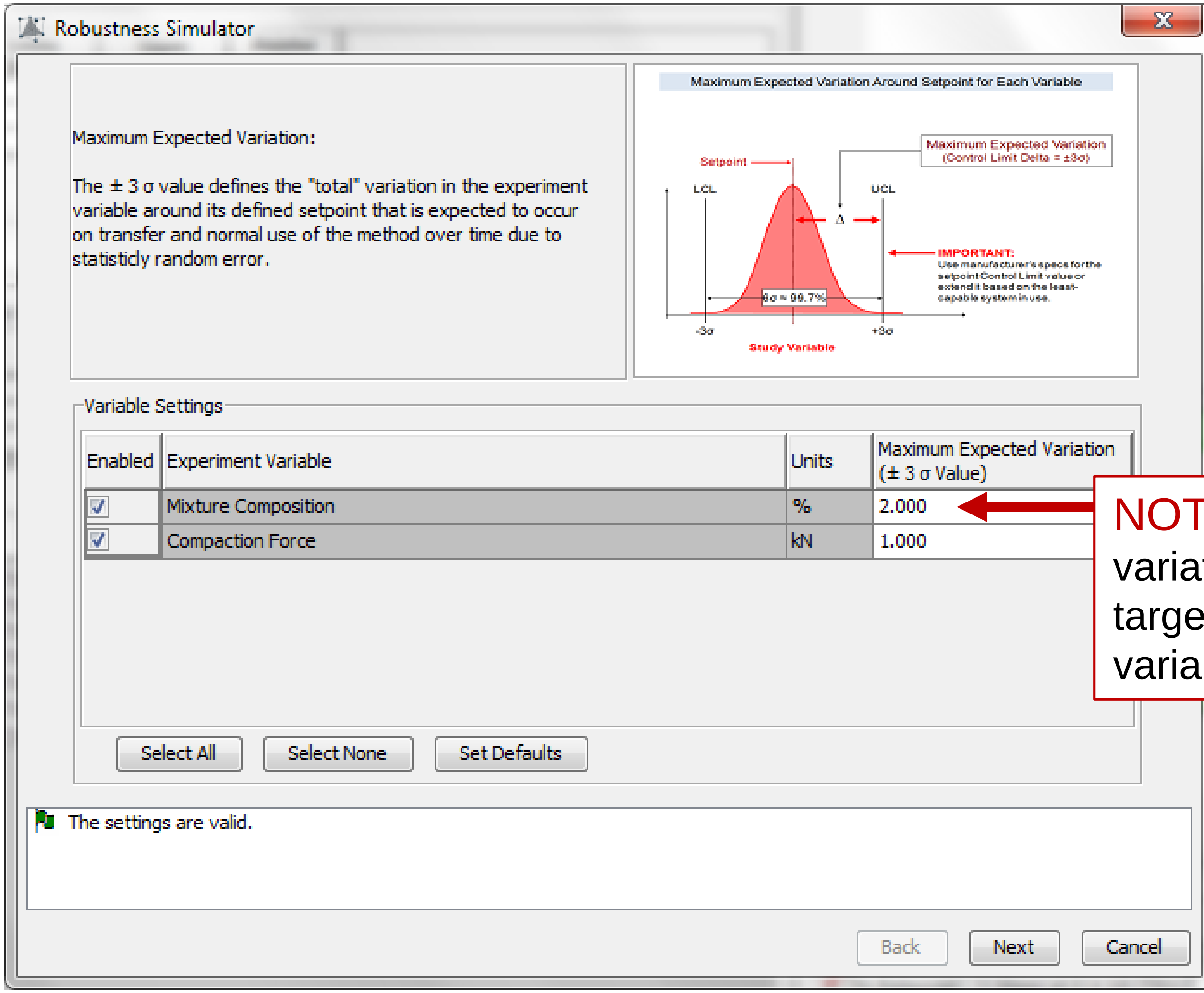


Unshaded Region With Predicted Best Settings:

Excipient 1 = 20%
Excipient 2 = 23%
Excipient 3 = 57%
Compaction Forve = 20 kN

S-Matrix®

Robustness Simulation – Expected Variation of CPPs



NOTE – Enter the expected variation (±3σ value) around target setpoint for each study variable.

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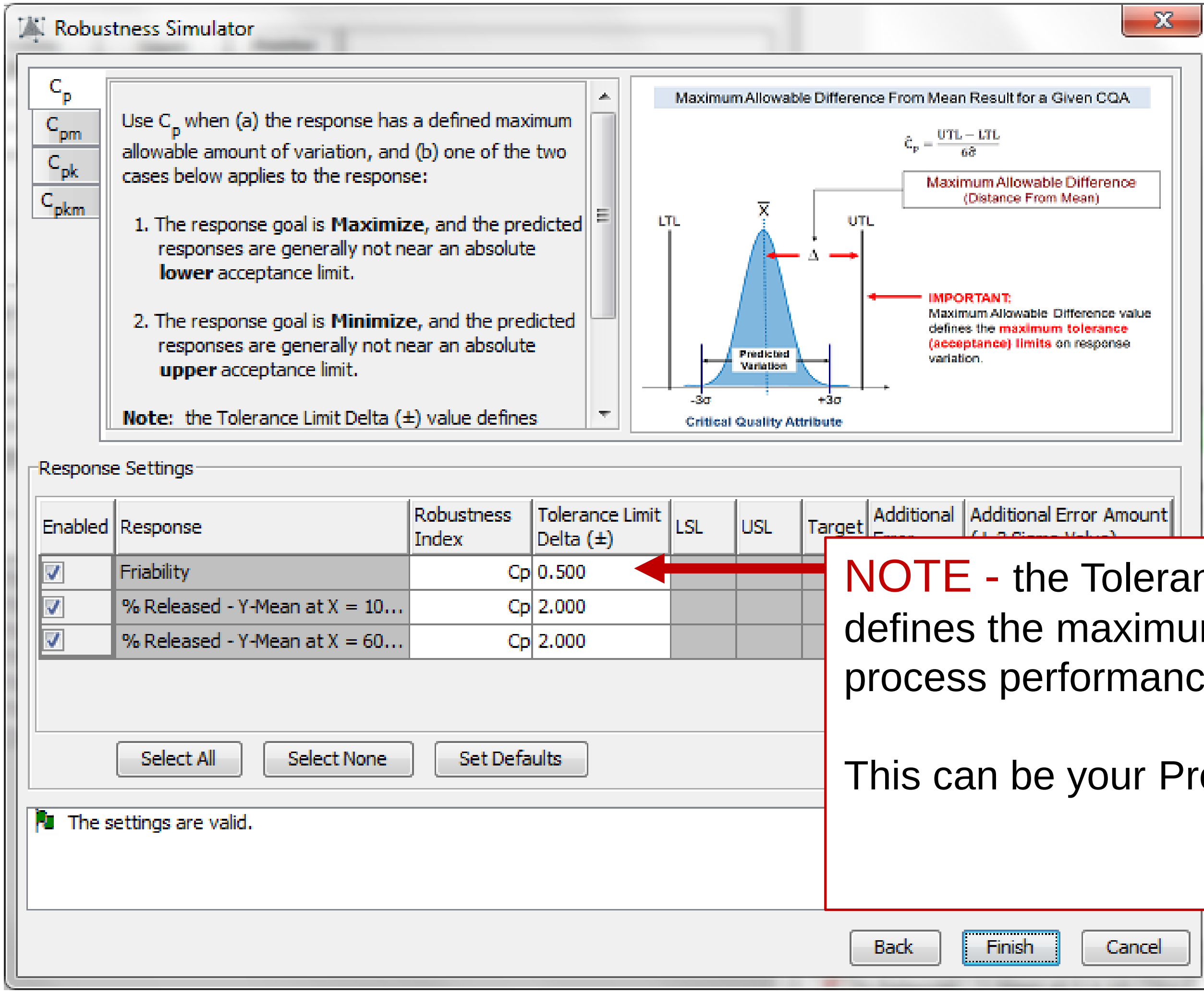
Robustness Simulation – Acceptable Variation Limits in CQAs



NOTE - the Tolerance Limit Delta (± value) defines the maximum acceptable limits on process performance variation.

This can be your Process Specification.

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Final Design and Operating Space – Mean Performance + Robustness

The software automatically visualizes the final robust design space.

Reports

Design and Operating Space - C.F. = 16.0

☑ Show Ternary Axis Lines

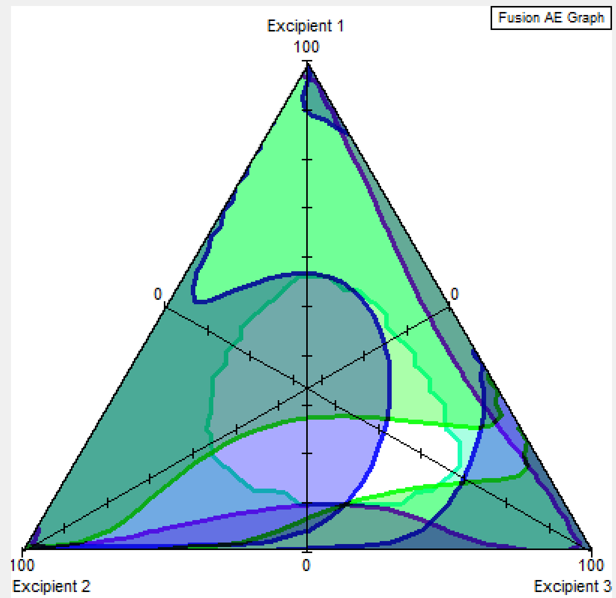
Graph Settings

	Name	Units	Lower Bound	Upper Bound	Pointer Coordinate
X1	Excipient 1	%	0.0	100.0	---
X2	Excipient 2	%	0.0	100.0	---
X3	Excipient 3	%	0.0	100.0	---

Compaction Force 16.00

☐ Operating Space Settings

Graph



Response Settings

	Name	Goal	Lower Bound	Upper Bound	Pointer Predictions	Contour Label	Color
☑	Friability	Minimize		1.00		☐	Red
☑	% Released - Y-Mean at X = 10 (TD1)	Target	8.00	12.00		☐	Blue
☑	% Released - Y-Mean at X = 60 (TD1)	Target	22.50	27.50		☐	Green
☑	Friability - Cp	Maximize	2.00			☐	Orange
☑	% Released - Y-Mean at X = 10 (TD1) - Cp	Maximize	2.00			☐	Teal
☑	% Released - Y-Mean at X = 60 (TD1) - Cp	Maximize	2.00			☐	Purple

Final Design and Operating Space – Mean Performance + Robustness

You can also zoom in and graphically represent your safe operating ranges, and the software will define verification runs to demonstrate that all performance goals are met.

Reports

Safe Operating Ranges

☑ Show Ternary Axis Lines

Graph Settings

	Name	Units	Lower Bound	Upper Bound	Pointer Coordinate
X1	Excipient 1	%	10.00	30.00	---
X2	Excipient 2	%	0.00	50.00	---
X3	Excipient 3	%	40.00	80.00	---

Compaction Force 20.00

Verification Run Settings

☑ Include Proven Acceptable Ranges (PARs)

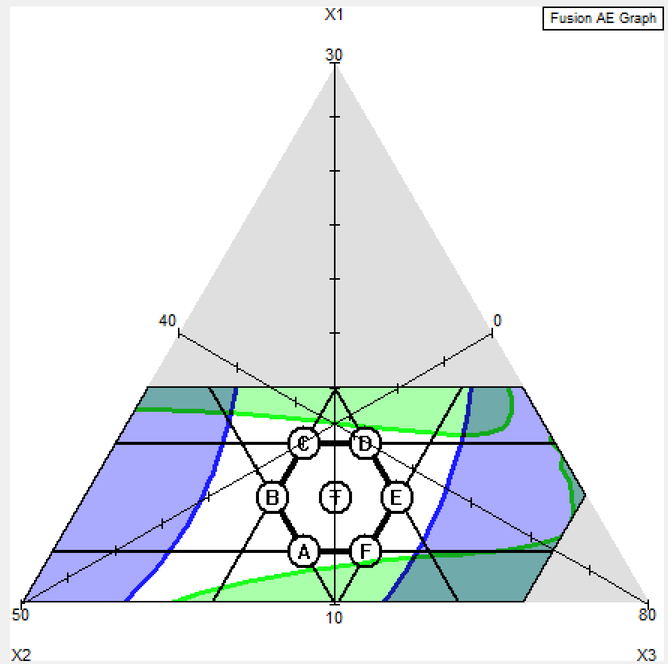
Operating Ranges Mixture Amount: 100.0 %

Variable	Lower Bound	Upper Bound
Excipient 1	15.00	25.00
Excipient 2	15.00	25.00
Excipient 3	55.00	65.00

Verification Runs ☑ Show Verification Run Labels

Point	Run ID	Excipient 1	Excipient 2	Excipient 3	Compaction Force	SUM
A	Safe_Operati	15.00	25.00	60.00	20.00	100.000
B	Safe_Operati	20.00	25.00	55.00	20.00	100.000
C	Safe_Operati	25.00	20.00	55.00	20.00	100.000
D	Safe_Operati	25.00	15.00	60.00	20.00	100.000
E	Safe_Operati	20.00	15.00	65.00	20.00	100.000
F	Safe_Operati	15.00	20.00	65.00	20.00	100.000
T	Safe_Operati	20.00	20.00	60.00	20.00	100.000

Graph



Response Settings

	Name	Goal	Lower Bound	Upper Bound	Target Predictions	Pointer Predictions	Contour Label	Co
☑	Friability	Minimize		1.00	0.33		☐	Red
☑	% Released - Y-Mean at X = 10 (TD1)	Target	8.00	12.00	9.74		☐	Blue
☑	% Released - Y-Mean at X = 60 (TD1)	Target	22.50	27.50	24.95		☐	Gre

S-Matrix®

Fusion Pro – QbD-aligned R&D Software

Case Study 2 – END