S-Matrix®

# Fusion QbD

## Fusion Process Development –

### Non-LC Method Development

### Formulation & Process R&D

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

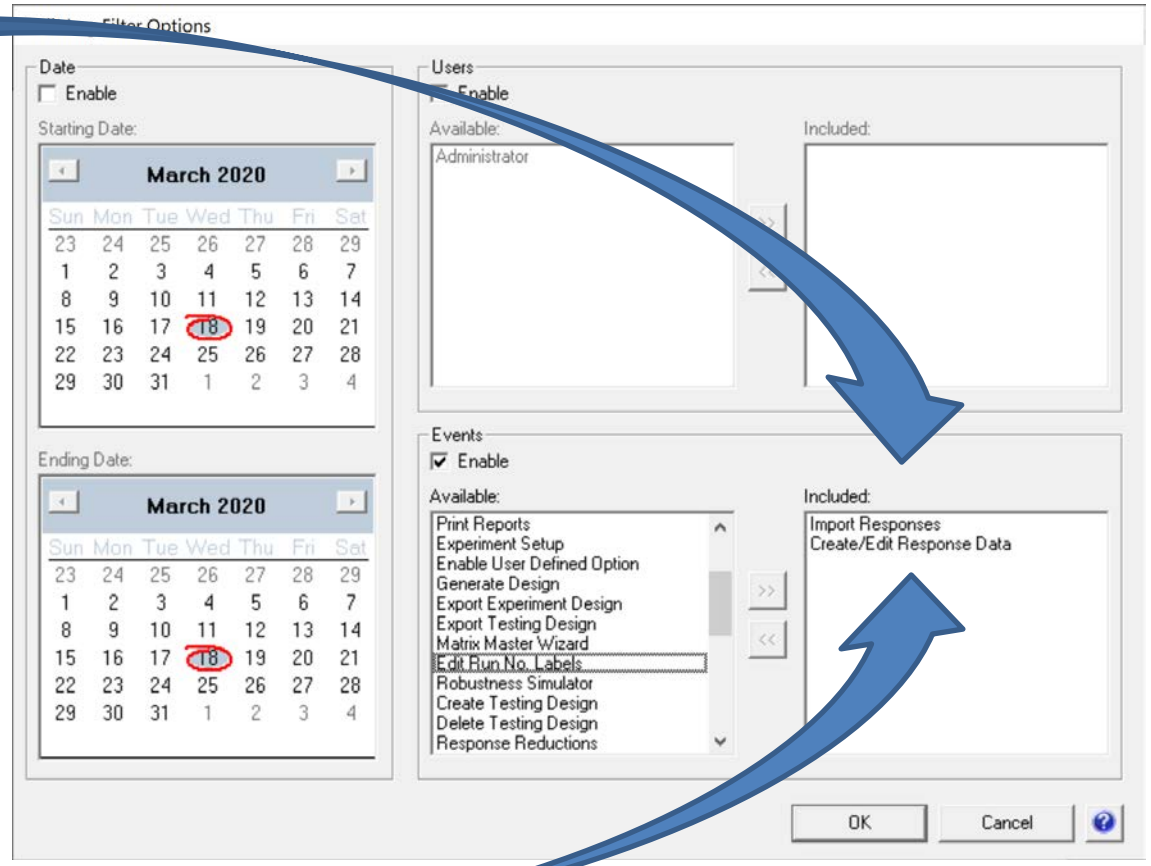
* – USP Workshop – Enhanced Approaches for Analytical Procedure Lifecycle: An Alternative to Traditional Validation (Sept. 24-25, 2018)

# 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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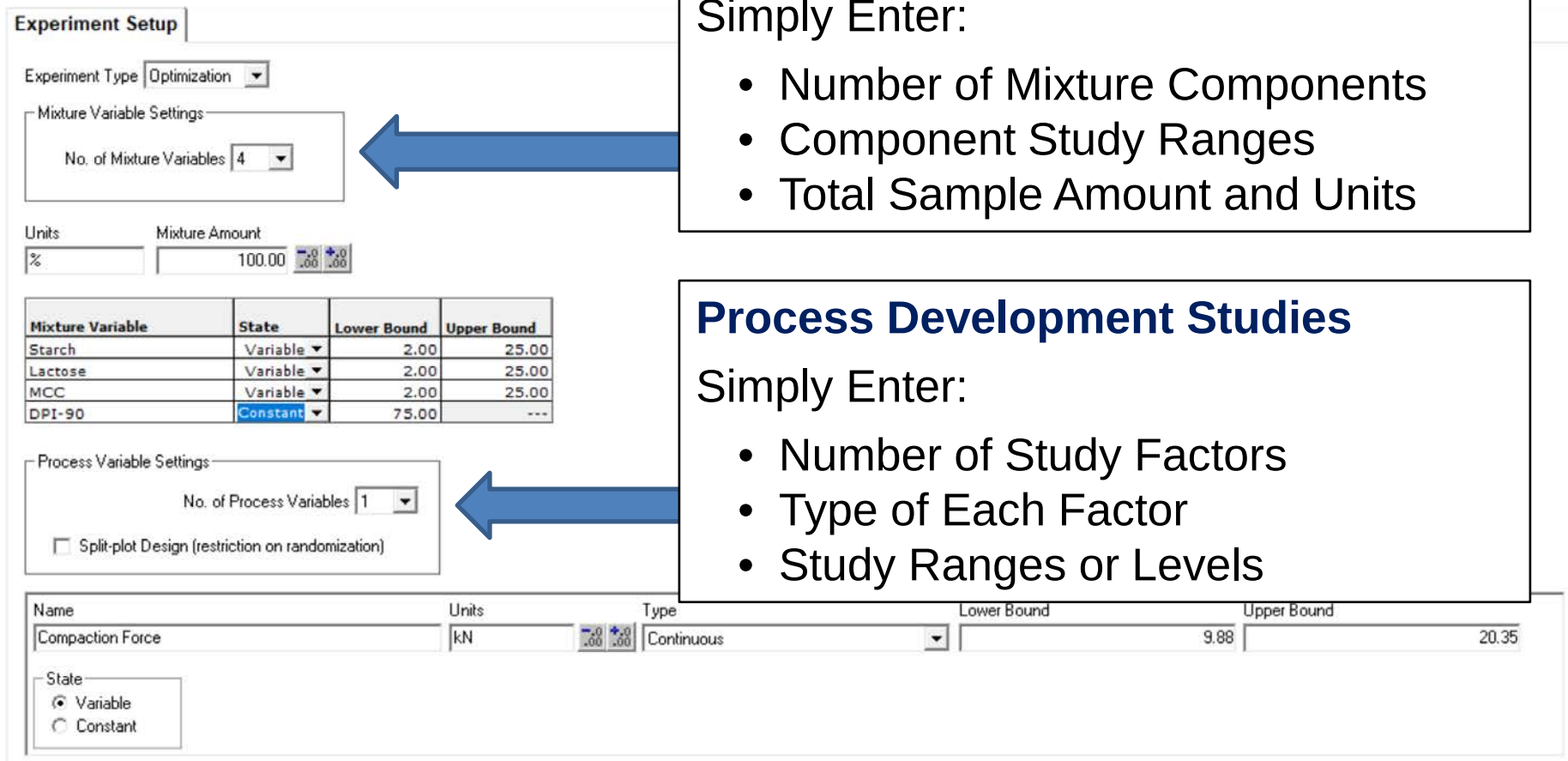
- Simplifies Handling of Complex Data ✓
- Integrated Monte Carlo Robustness ✓
- Full QbD Reporting ✓

# 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:

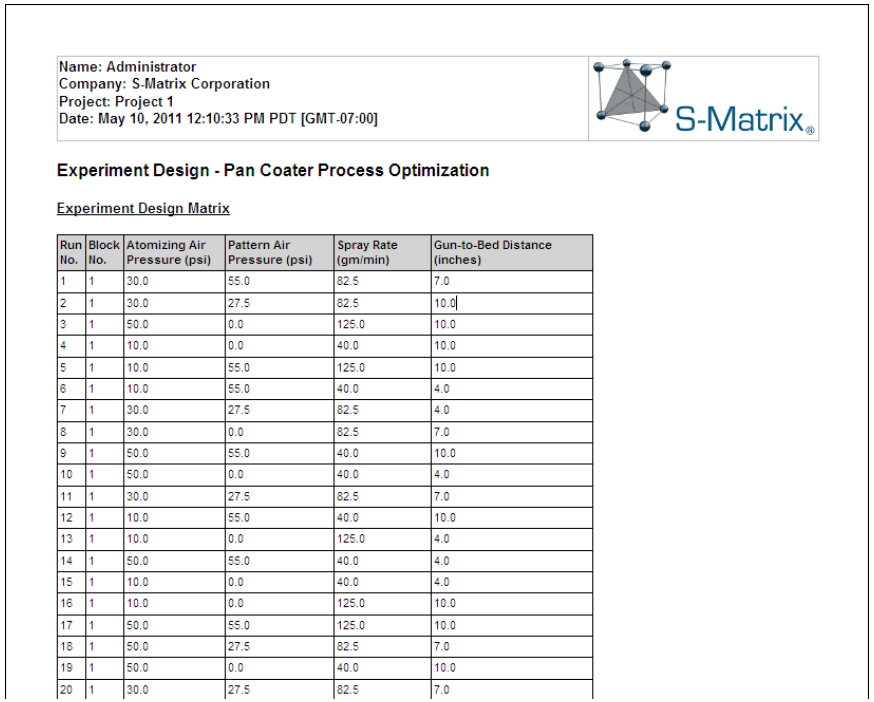
- Number of Study Factors
- Type of Each Factor
- Study Ranges or Levels

## 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

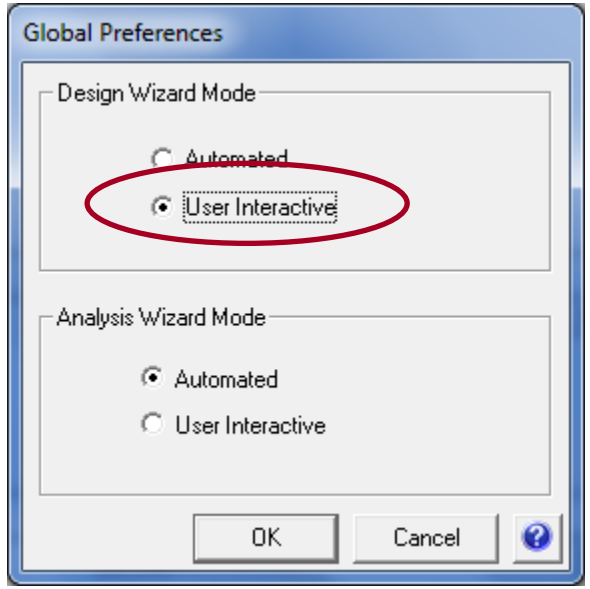
| Run No. | Block No. | Atomizing Air Pressure (psi) | Pattern Air Pressure (psi) | Spray Rate (gm/min) | Gun-to-Bed Distance (inches) |
|---|---|---|---|---|---|
| 1 | 1 | 30.0 | 55.0 | 82.5 | 7.0 |
| 2 | 1 | 30.0 | 27.5 | 82.5 | 10.0 |
| 3 | 1 | 50.0 | 0.0 | 125.0 | 10.0 |
| 4 | 1 | 10.0 | 0.0 | 40.0 | 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 |

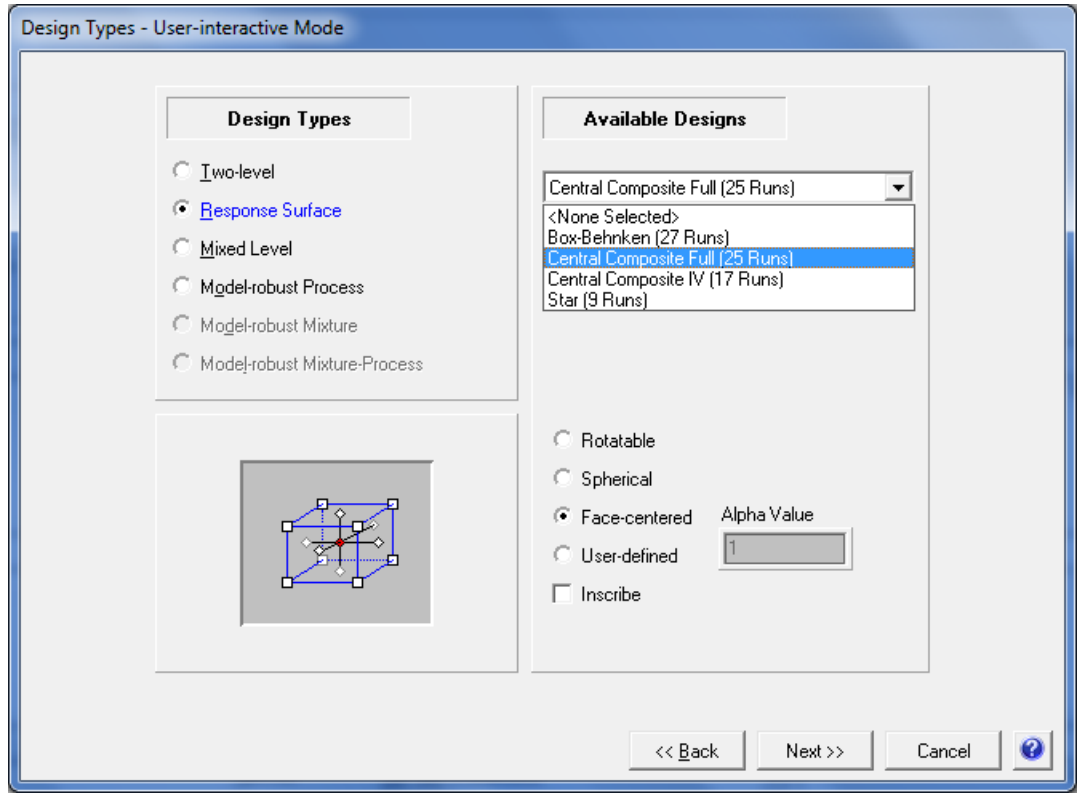
### Automated Design Logic Accounts for:

- **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

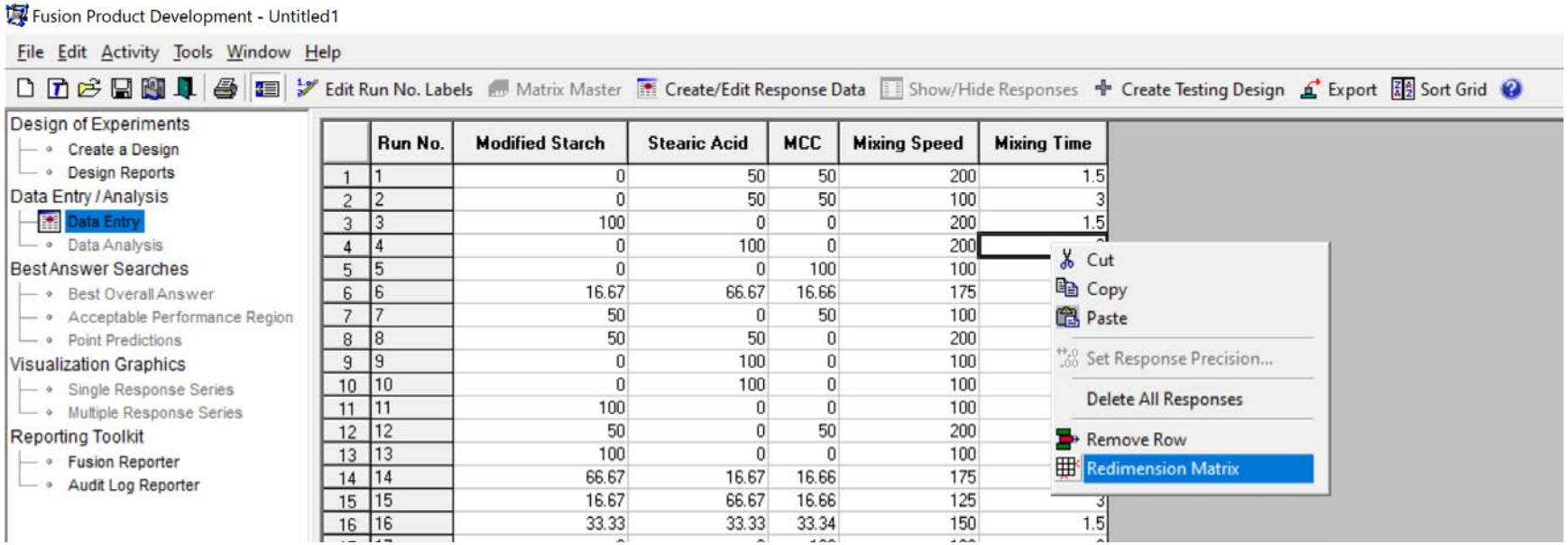
- **DOE Expert Users**
- **Users Following an SOP**



# 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 |

# Key Benefits of Fusion Process Development

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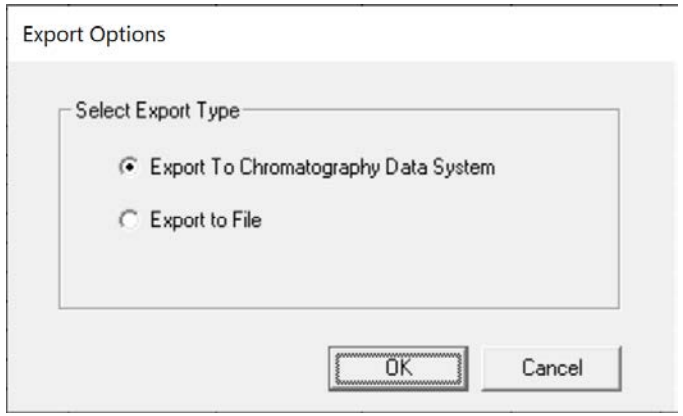
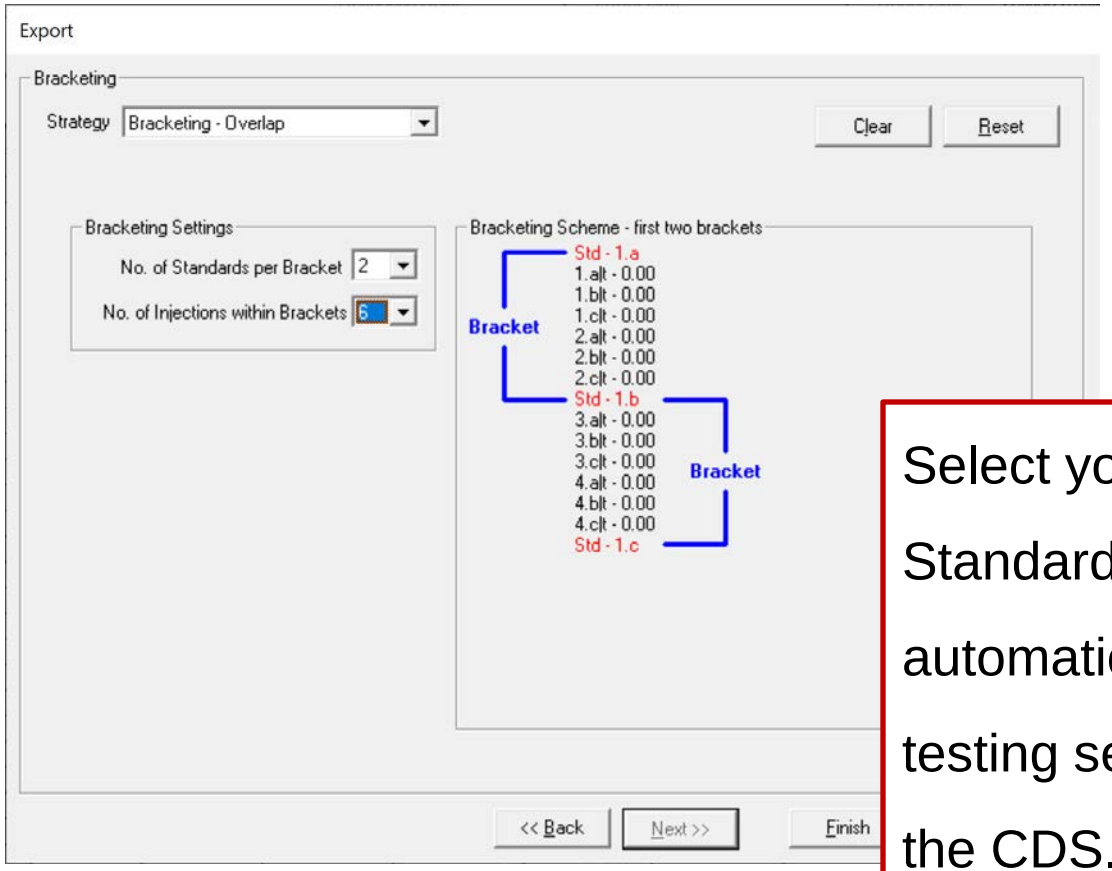
- Flexible, Automated (1-Click) Design ✓
- **Full LC Testing Automation** ✓
- Simplifies Handling of Complex Data ✓
- Integrated Monte Carlo Robustness ✓
- Full QbD Reporting ✓

# Export Testing Design Sequences to the CDS

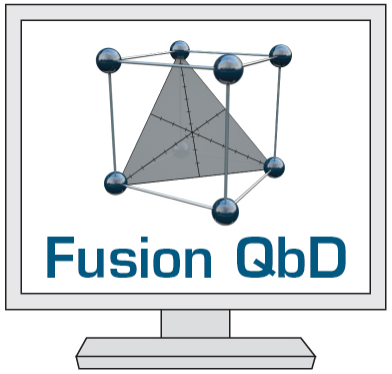
## Standards Protocol Setup Wizard




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

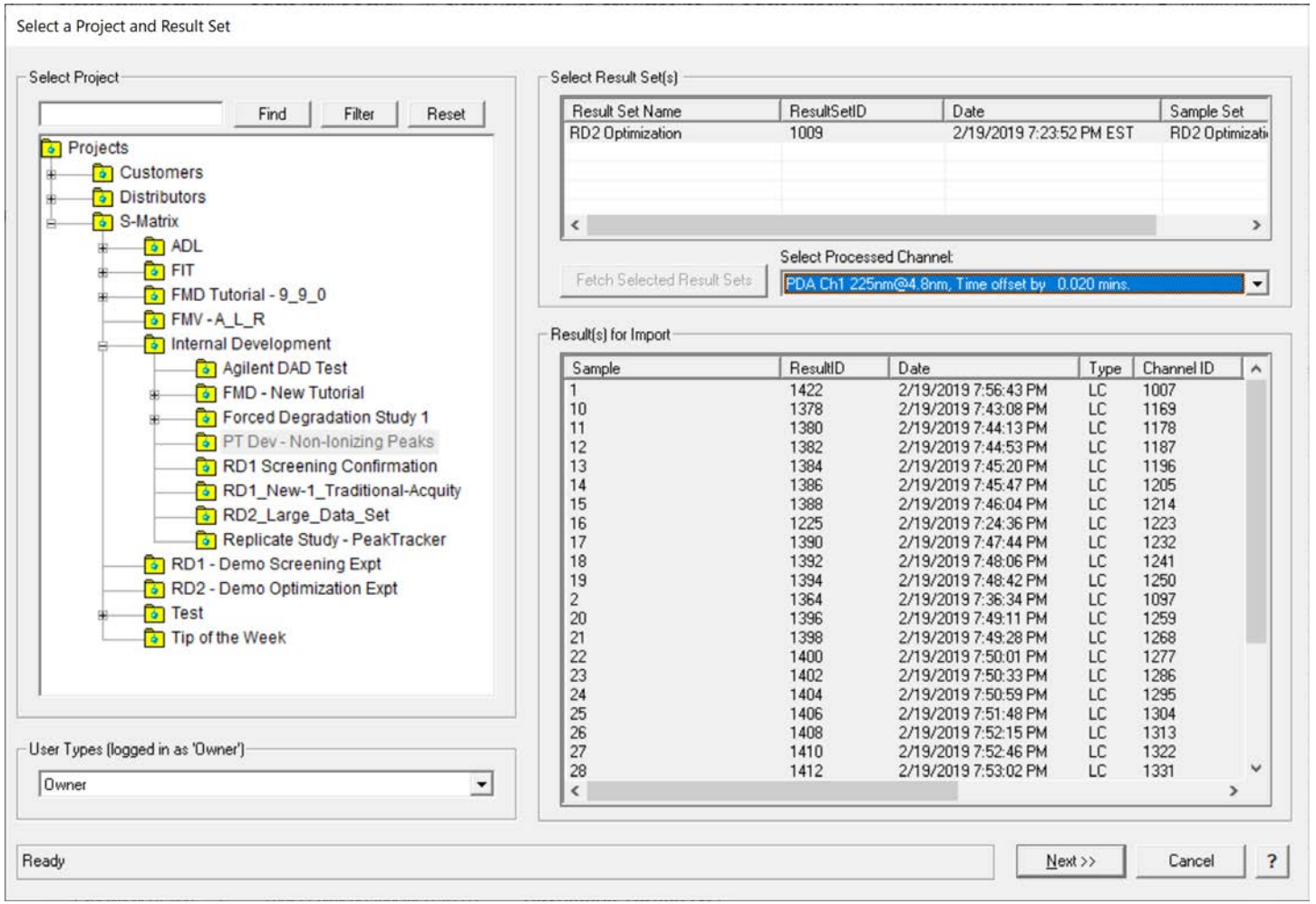
File Edit View Help

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 | | | |

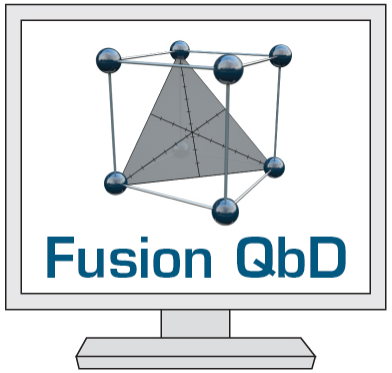
**Automated, Audited Data Exchange Preserves Data Integrity**

# Import All Required Results Data from CDS



# Import All Required Results Data from CDS

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

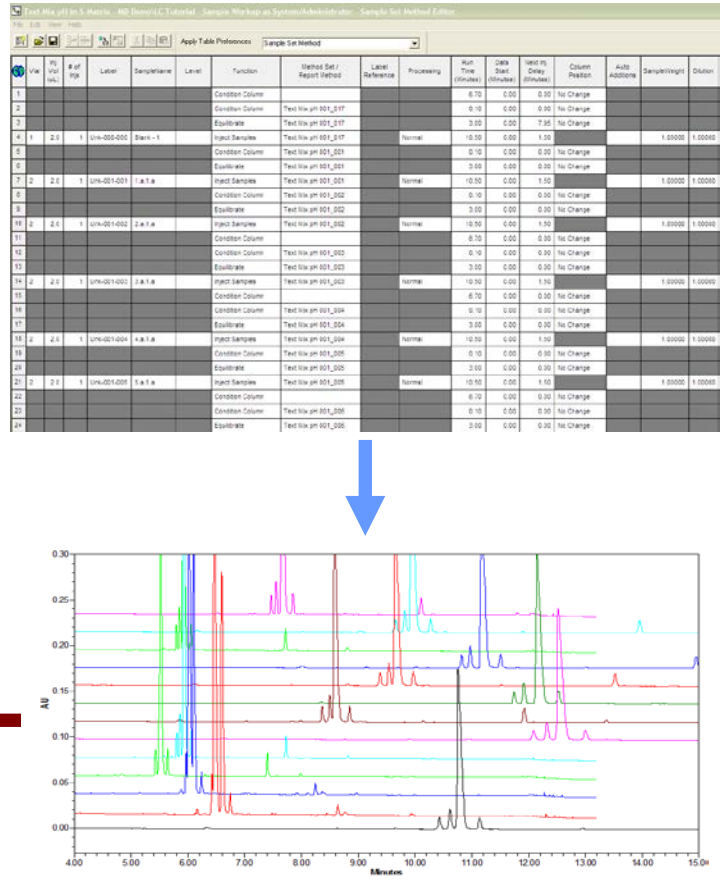



Automatically Retrieve All Chromatogram Results Da

Automated analysis, graphing, and reporting.

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

## Chromatography Data Software (CDS)



**Automated, Audited Data Exchange Preserves Data Integrity**

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- Integrated Monte Carlo Robustness ✓
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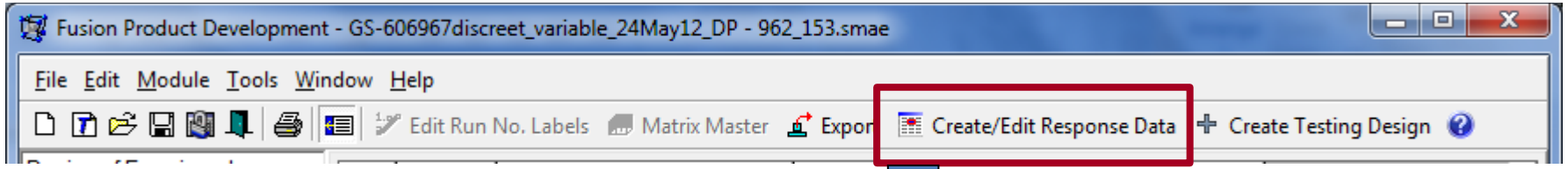
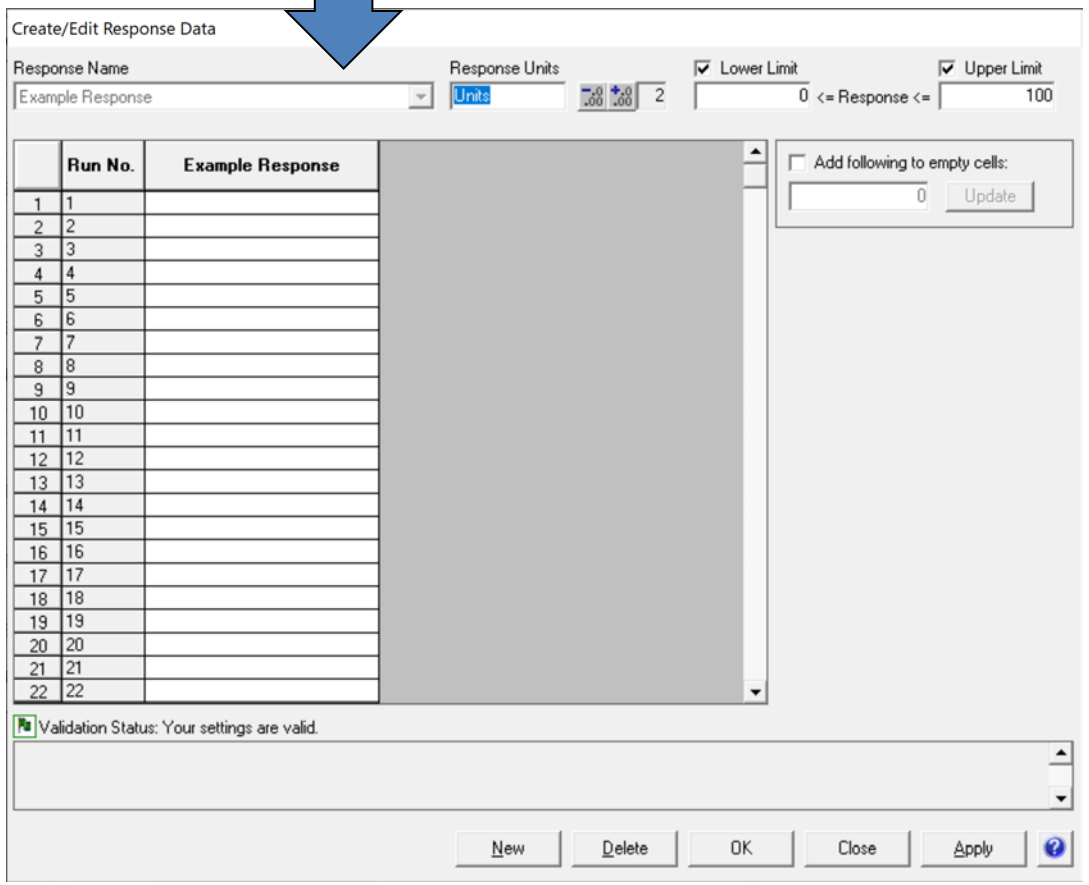
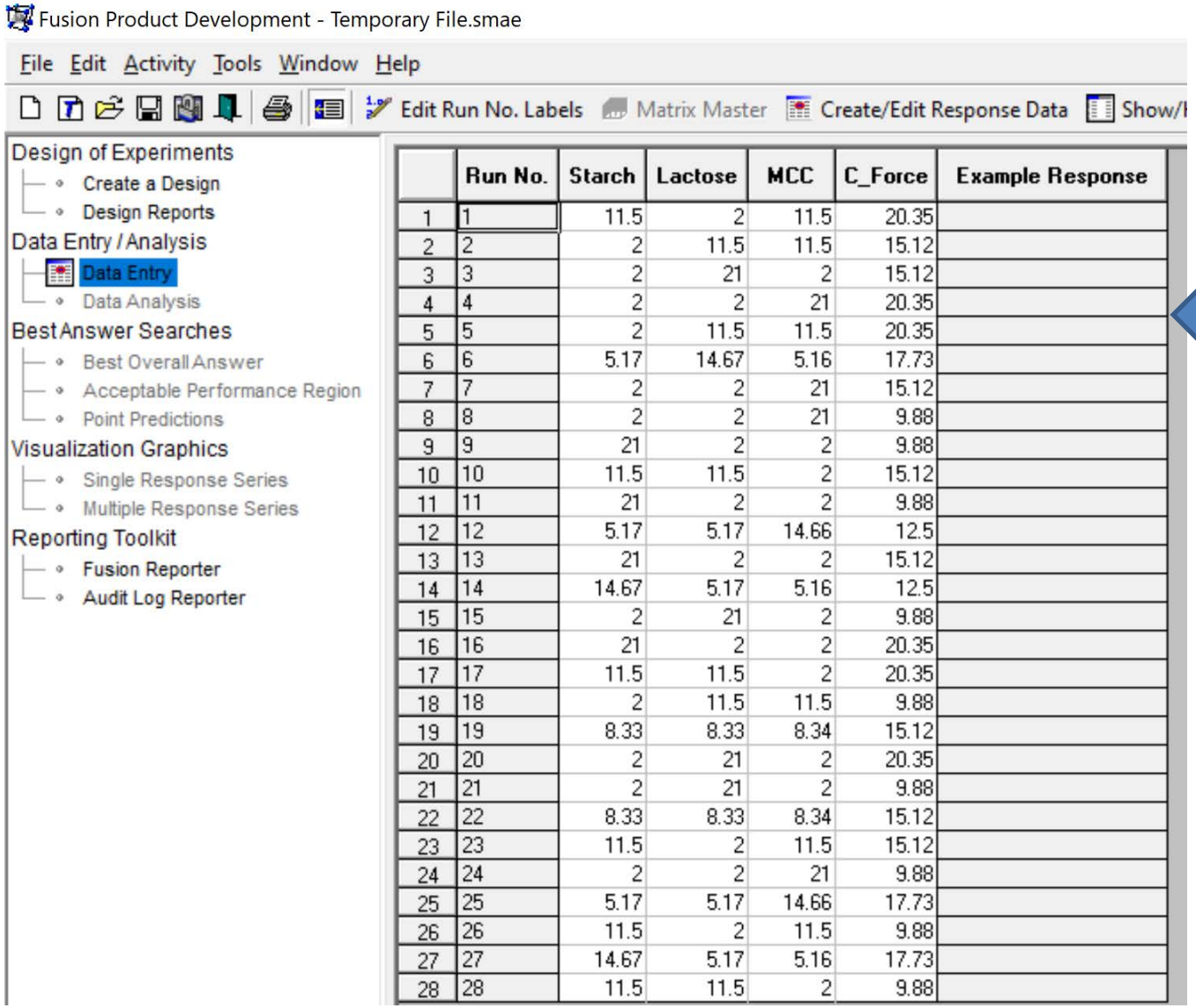
# Simple Data Entry – One Test Result Per Run




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



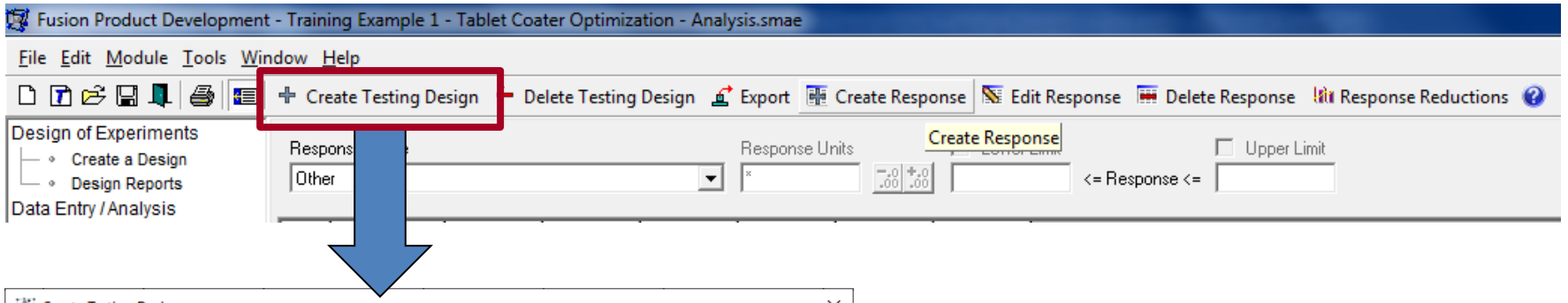
# Simple Data Entry – One Test Result Per Run

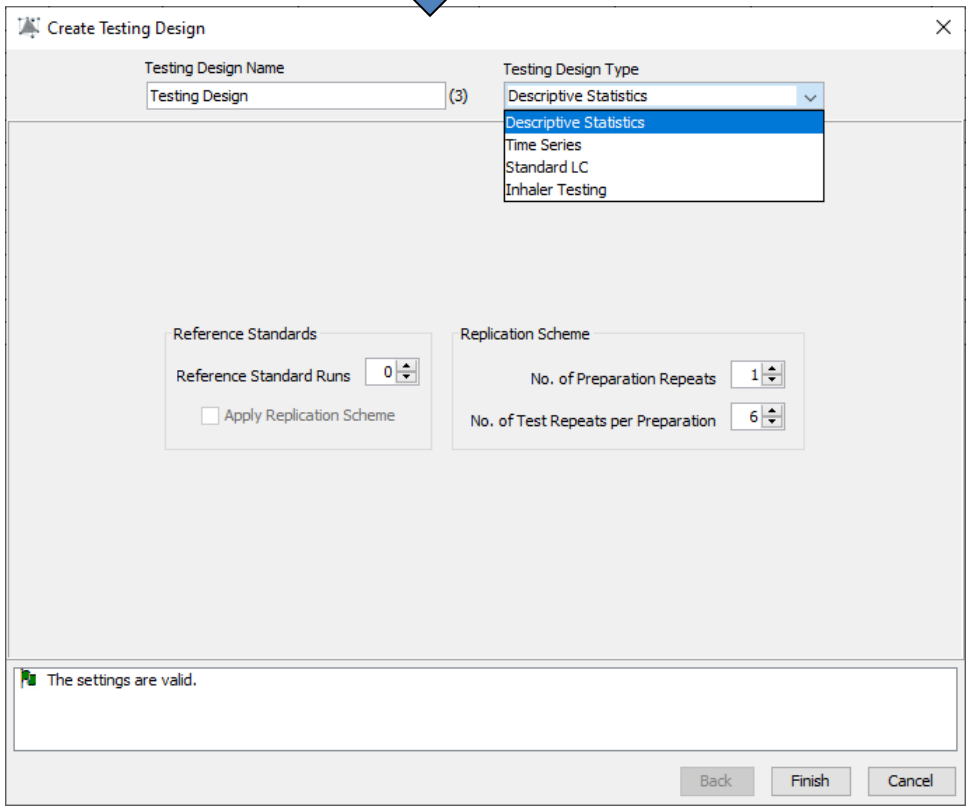



| | Run No. | Starch | Lactose | MCC | C_Force | Example Response |
|---|---|---|---|---|---|---|
| 1 | 1 | 11.5 | 2 | 11.5 | 20.35 | |
| 2 | 2 | 2 | 11.5 | 11.5 | 15.12 | |
| 3 | 3 | 2 | 21 | 2 | 15.12 | |
| 4 | 4 | 2 | 2 | 21 | 20.35 | |
| 5 | 5 | 2 | 11.5 | 11.5 | 20.35 | |
| 6 | 6 | 5.17 | 14.67 | 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.

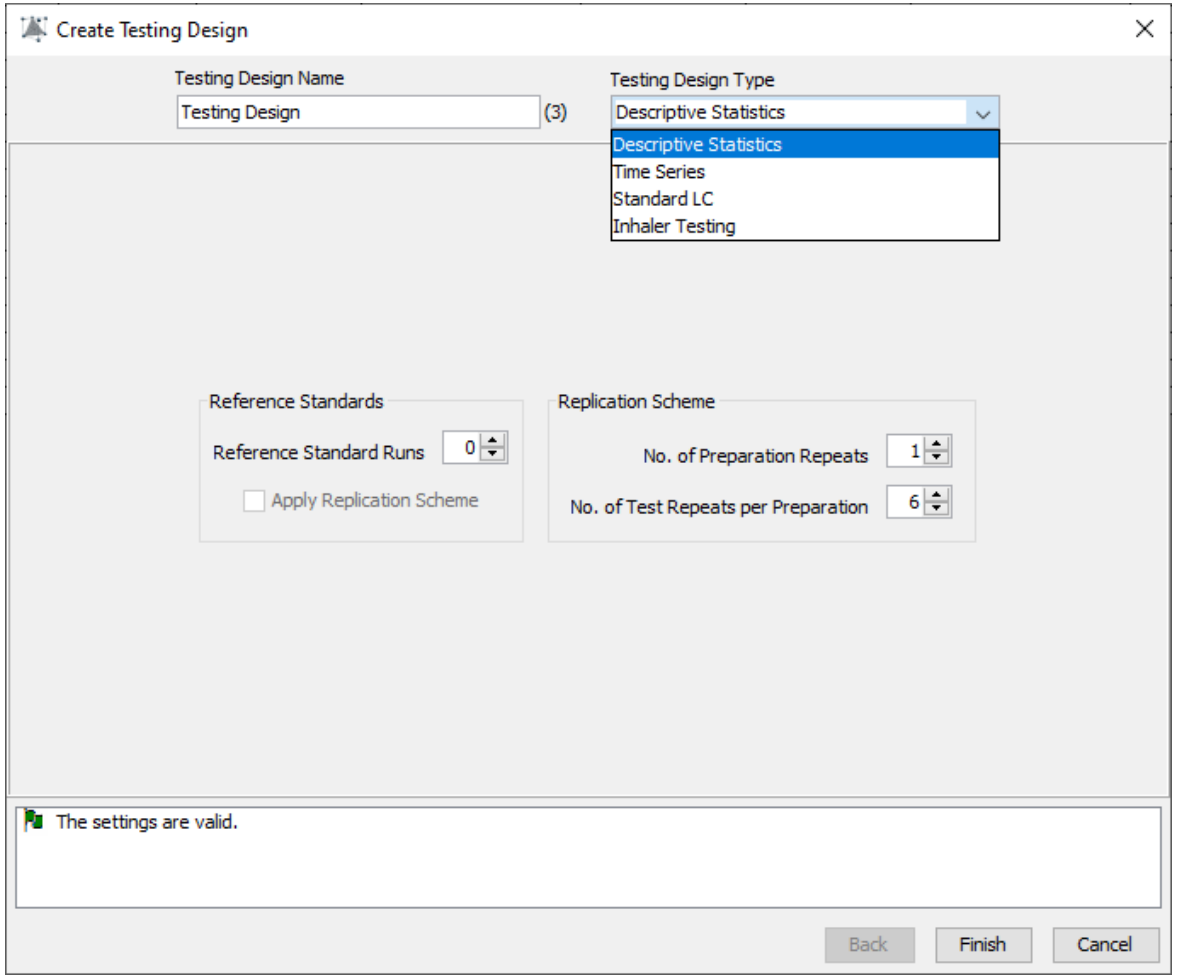
# Response Data Handler™ Wizards

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

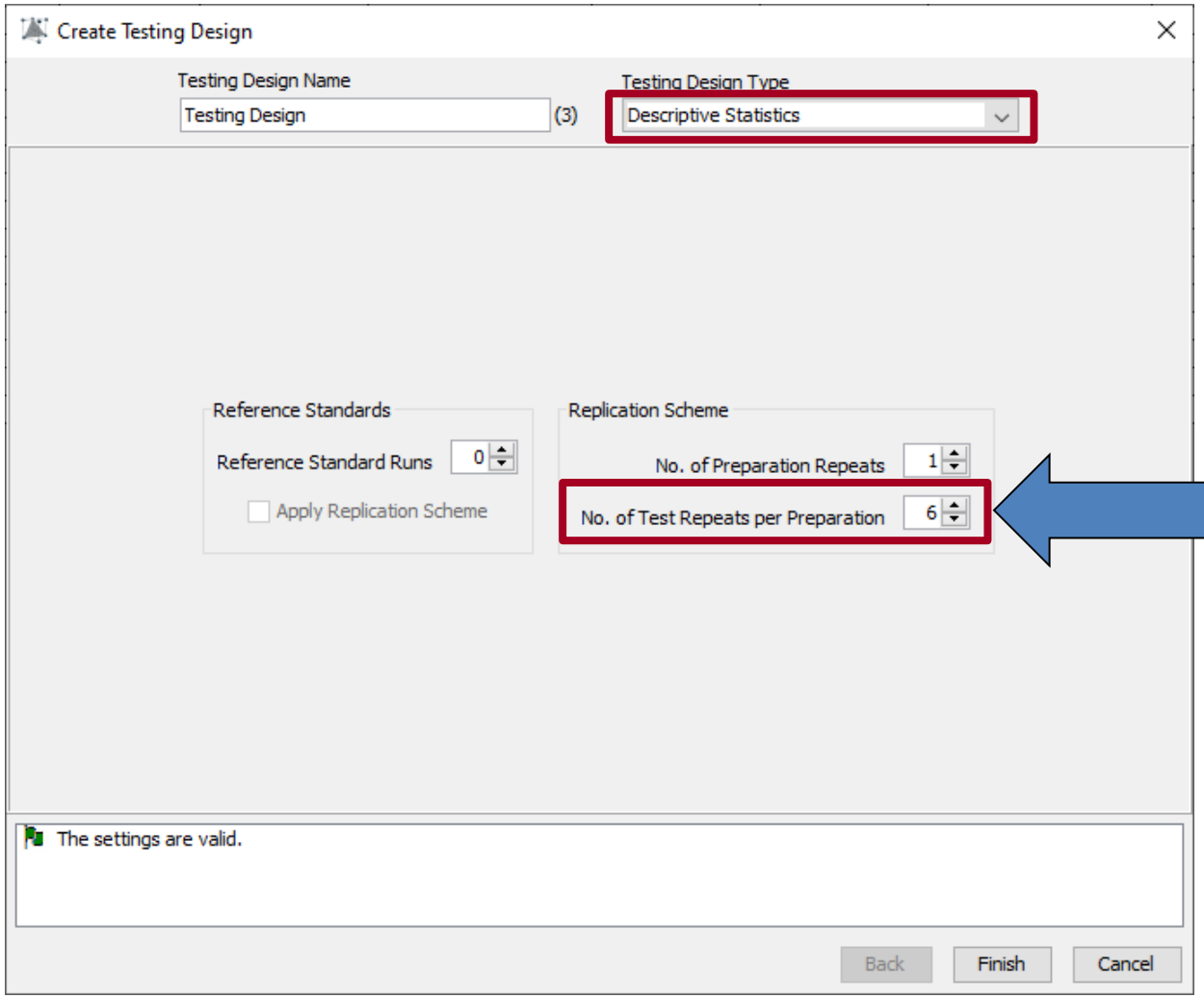
## Handle Complex Data Simply and Easily!

### 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

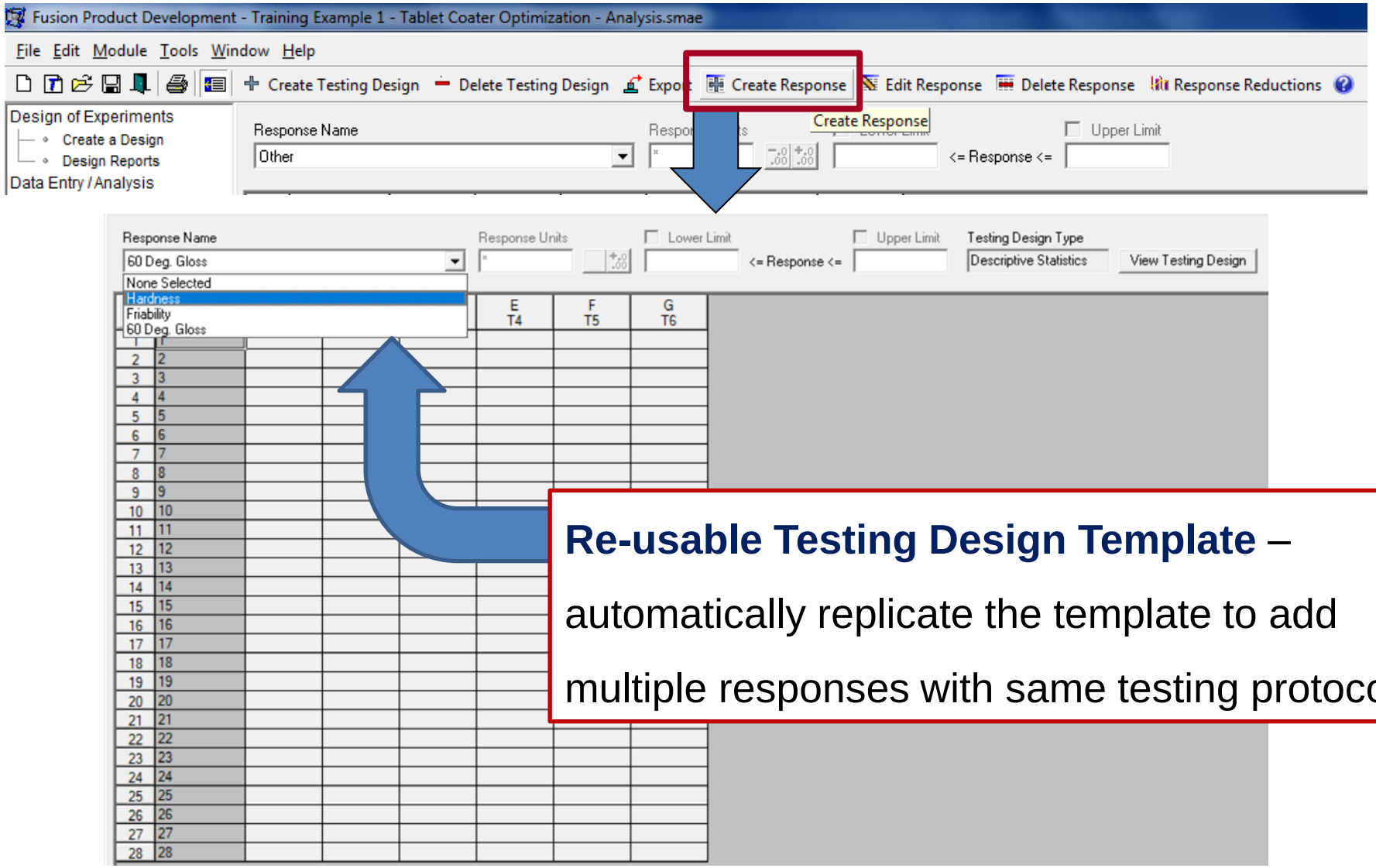



**Example Protocol –**

Test six (6) tablets for physical properties:

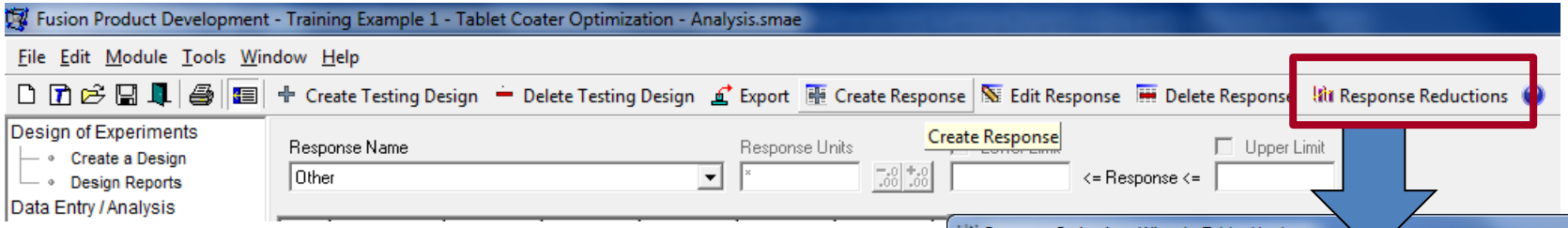
- Hardness
- Friability
- Gloss
- …

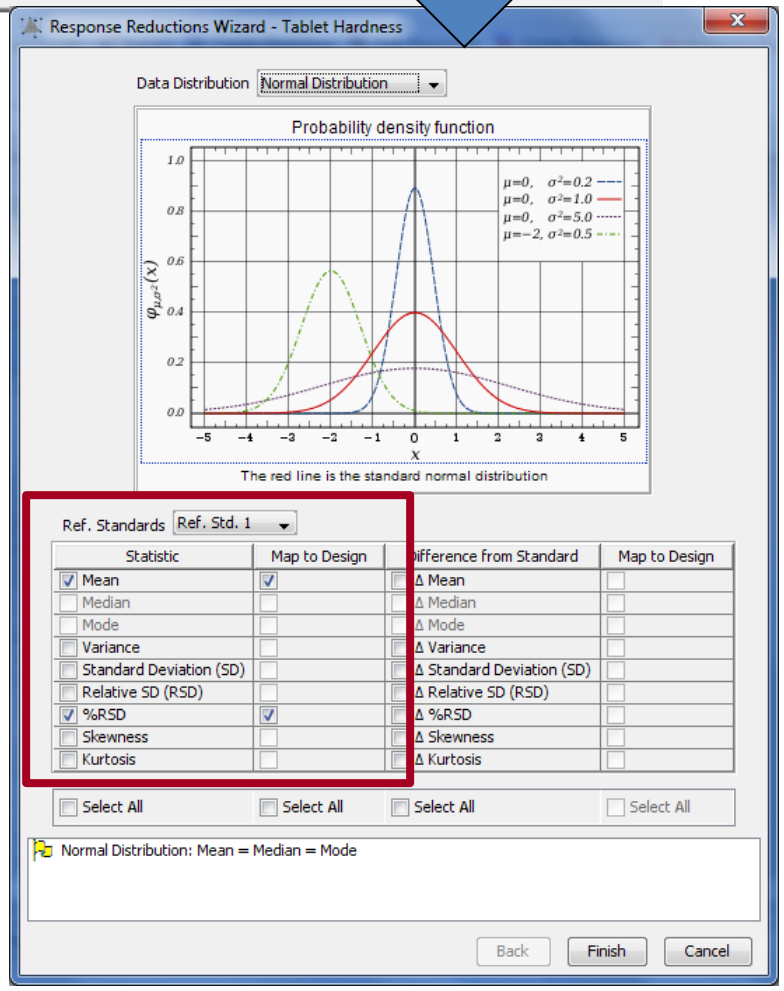
# Descriptive Statistics – Testing Template




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

# Descriptive Statistics – Automated Response Generation

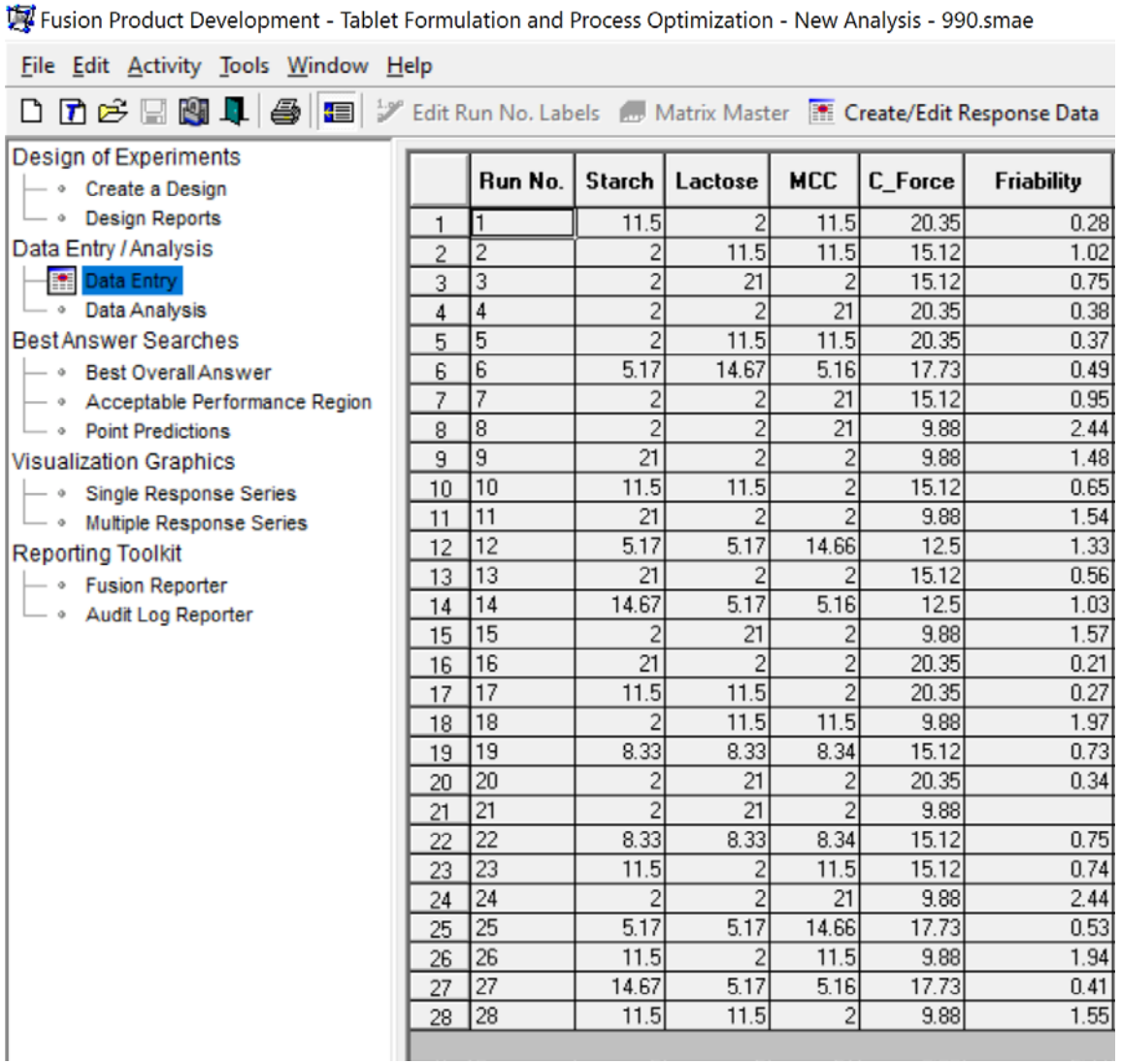



**Automated Response Reductions:**

- 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

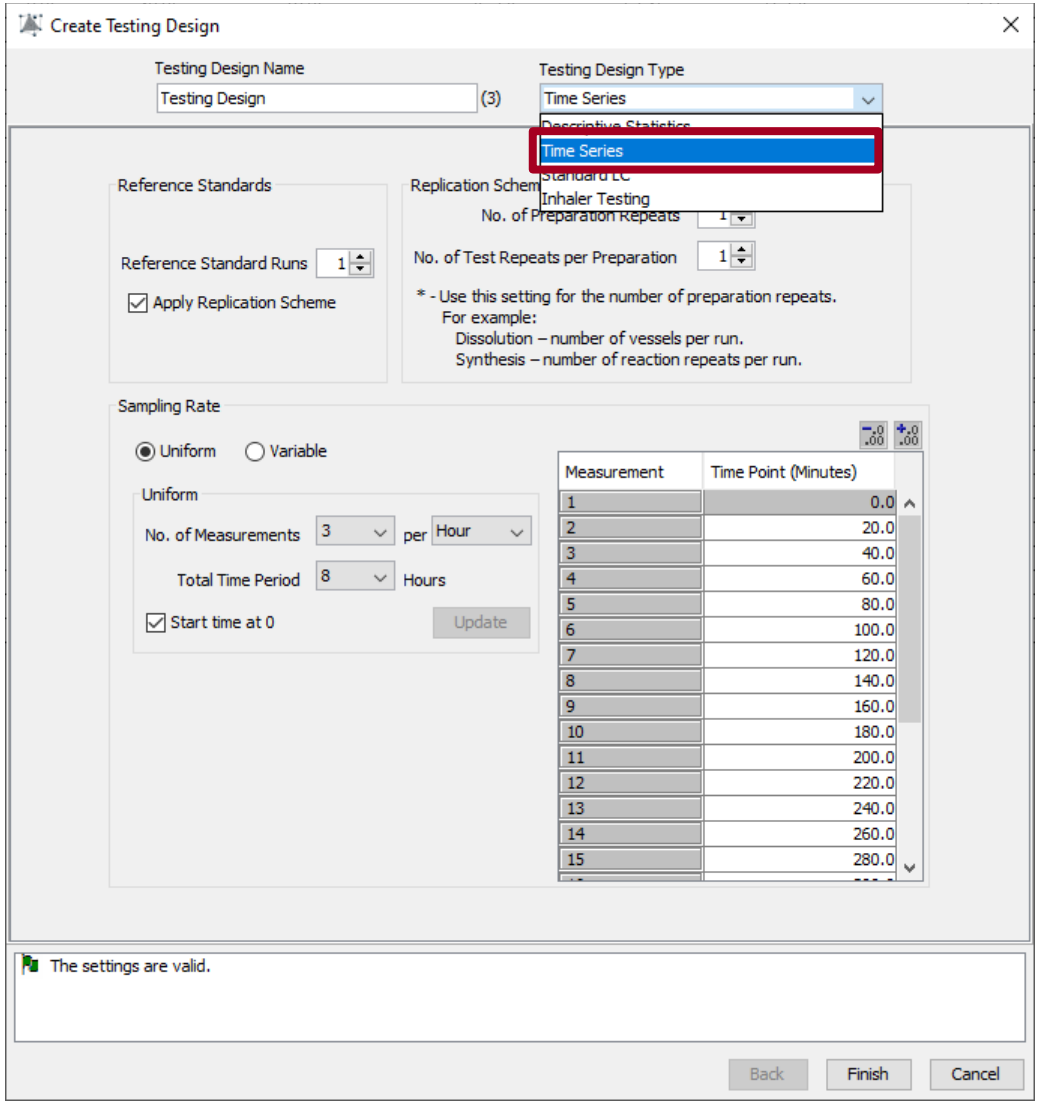
# Descriptive Statistics – Automated Response Generation




| | 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

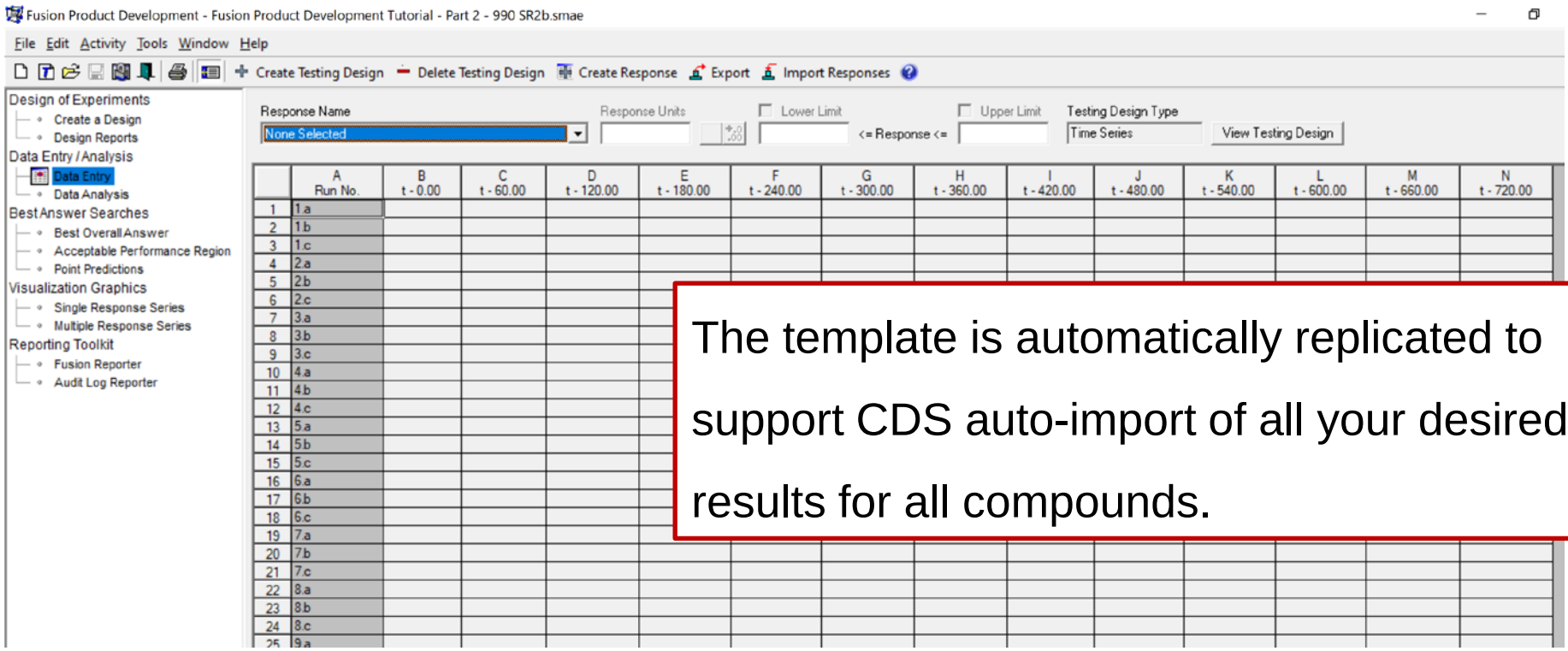
**Time Series – Instant Testing Protocol**

**Supports:**

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

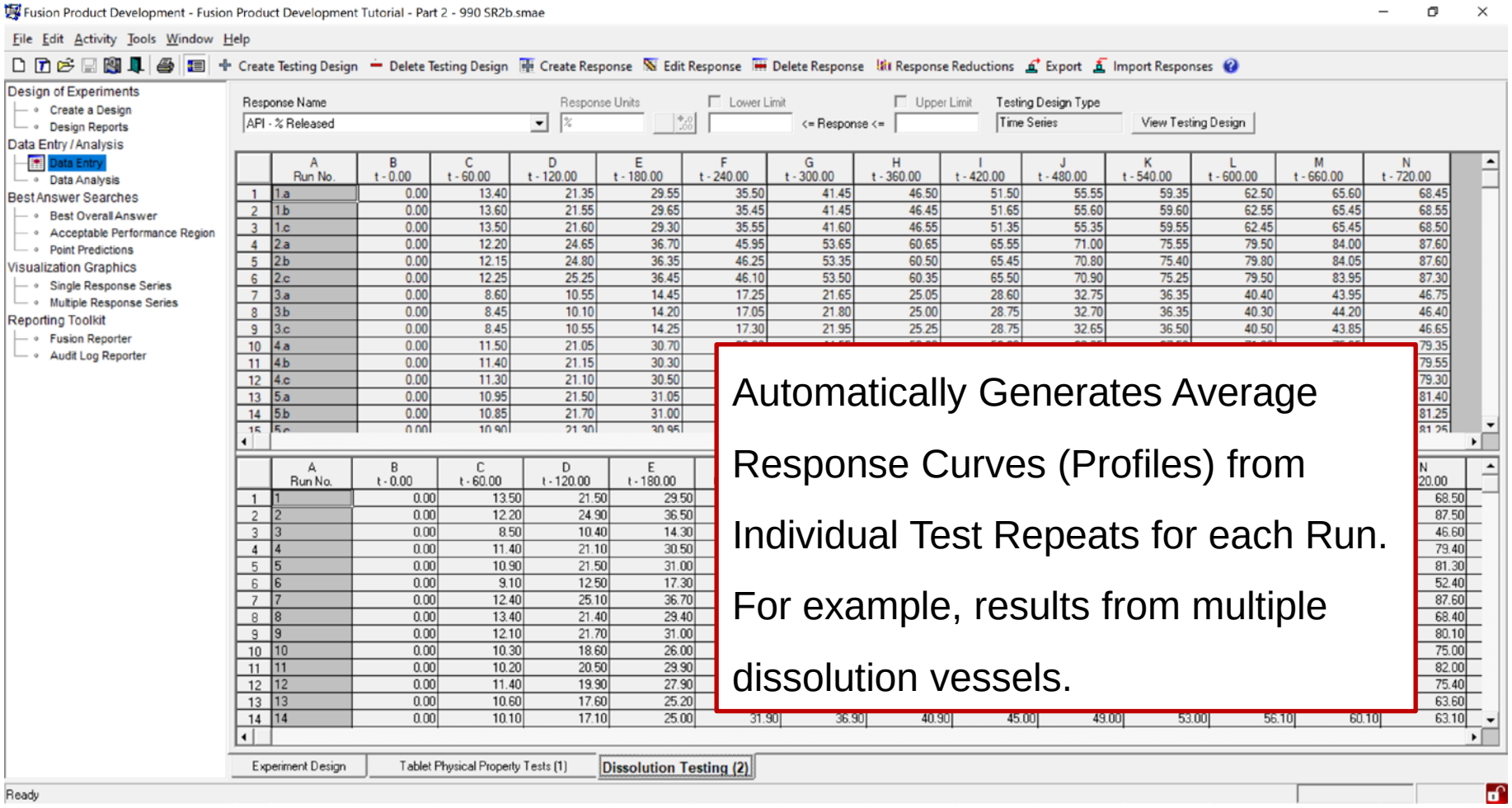
# Time Series – Testing Template

## Re-usable Testing Design Template



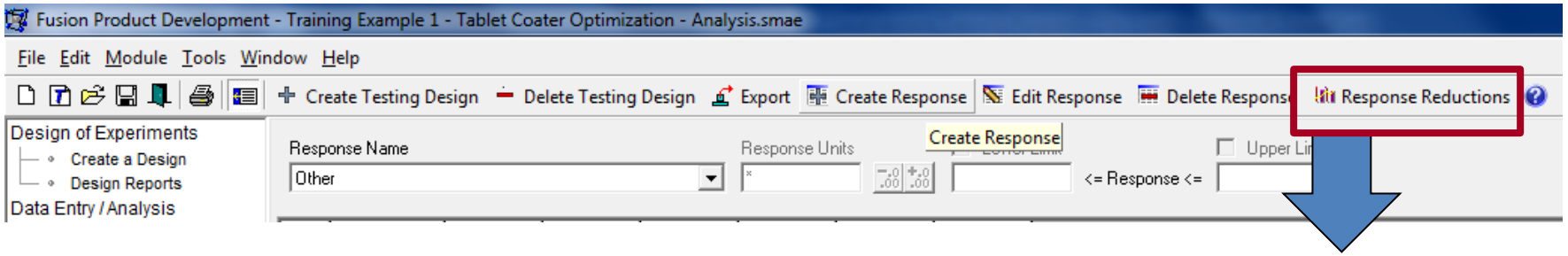

The template is automatically replicated to support CDS auto-import of all your desired results for all compounds.

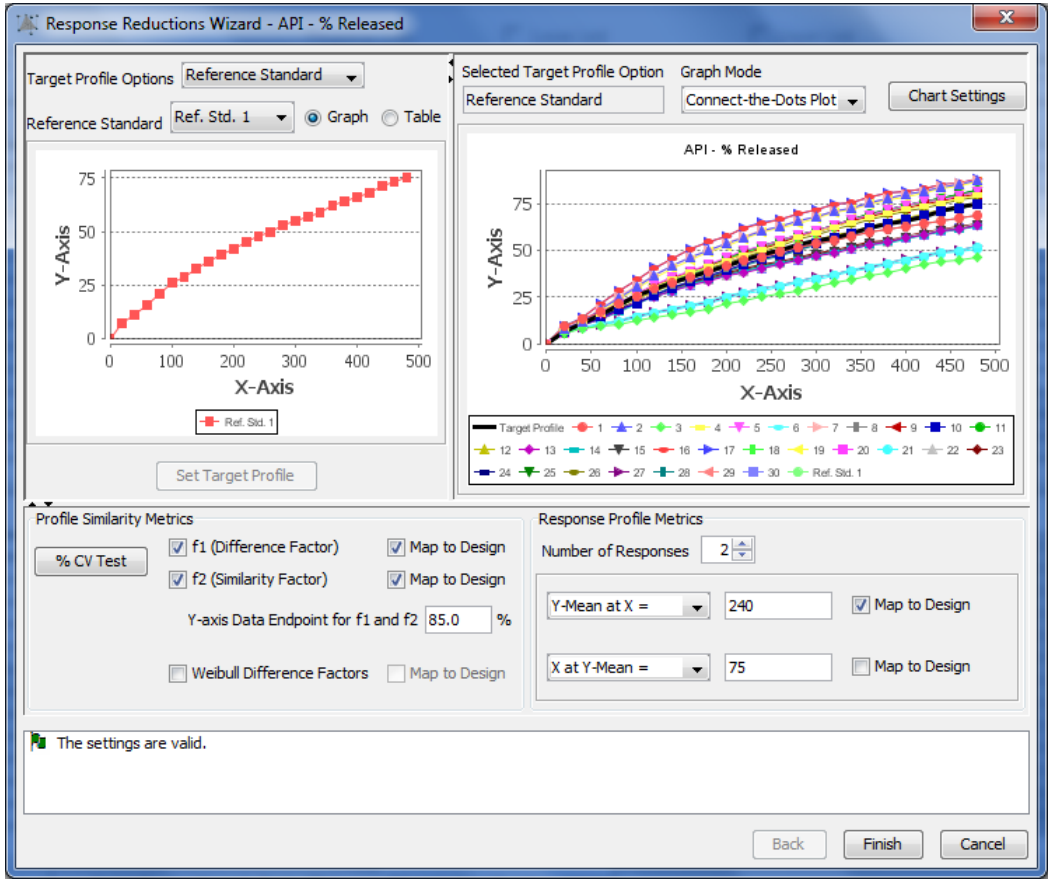
# Time Series – Multiple Time Point Tests per Run




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



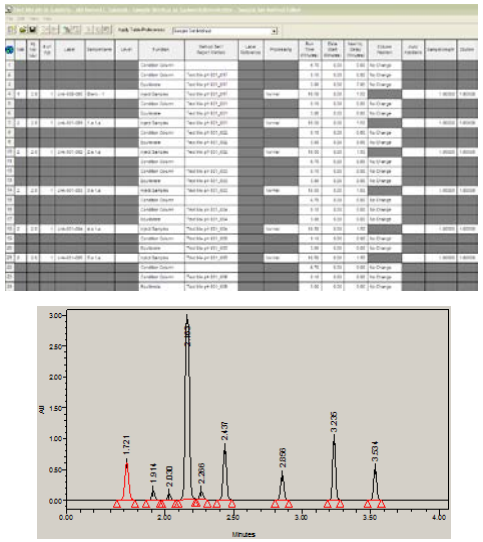



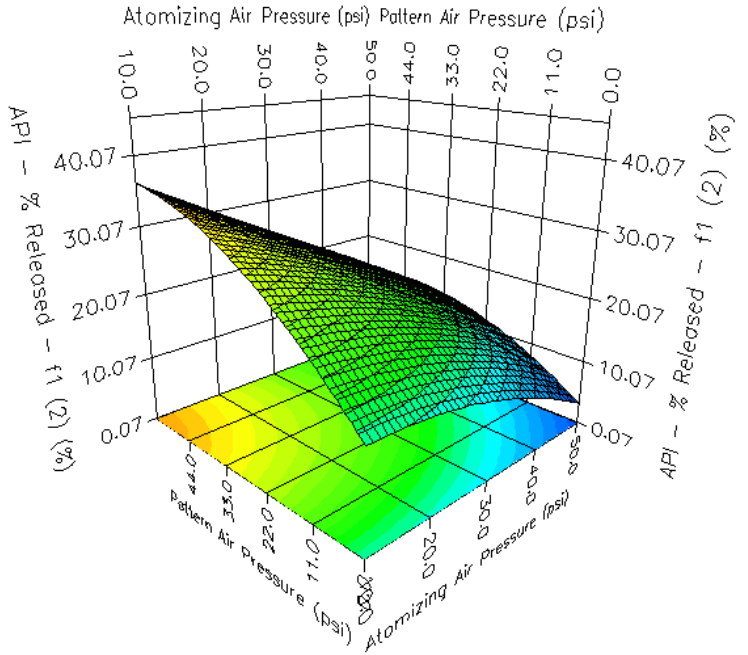

**Coordinated Response Reductions:**

- 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

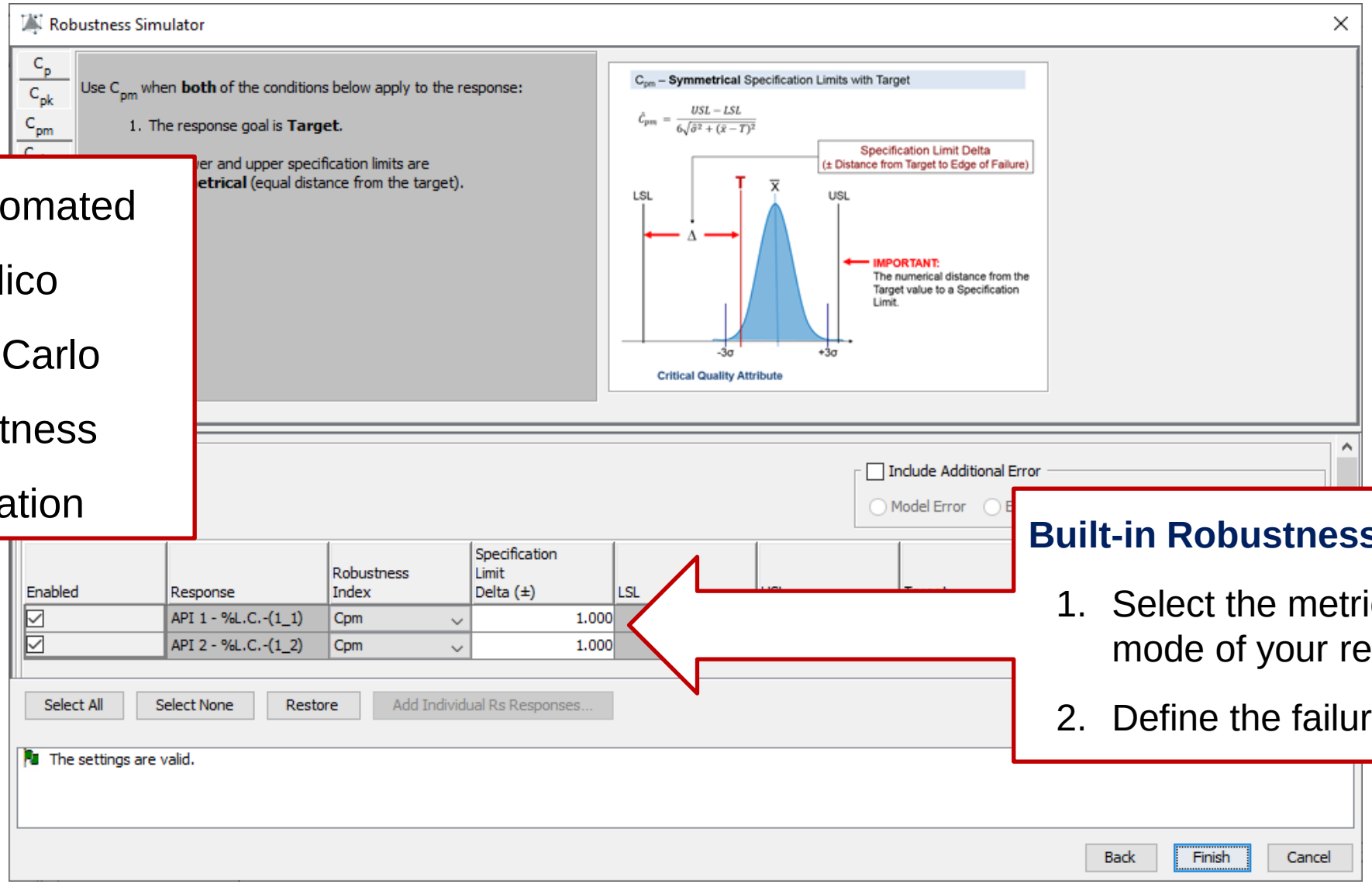
Fully Automated

In-silico

Monte Carlo

Robustness

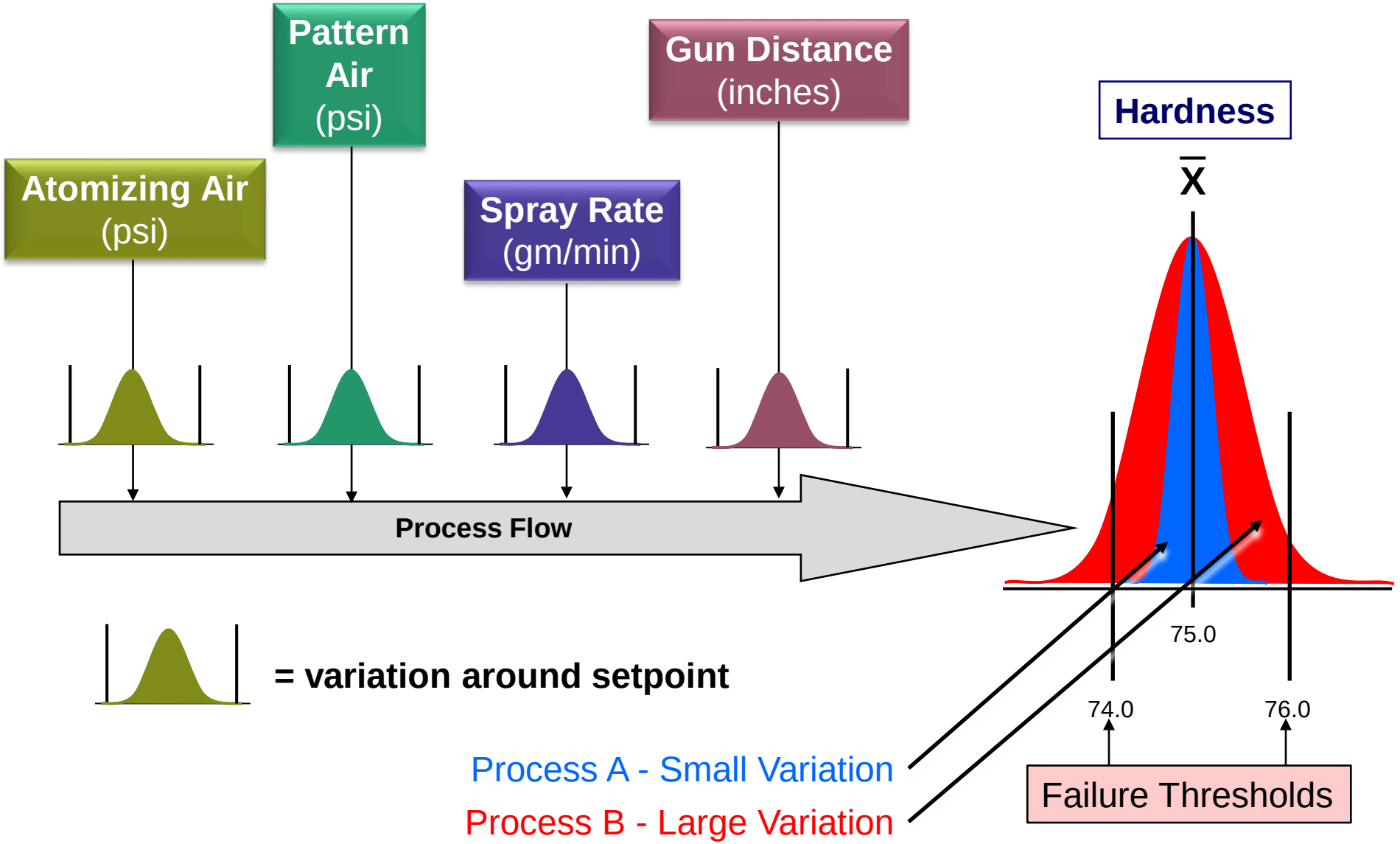
Simulation




## 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 Mean Performance Failure – Hardness

Region of Robustness Failure – % Released


| | 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.)

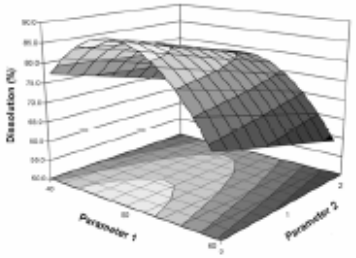



Figure 1a: Response surface plot of dissolution as a function of two parameters of a granulation operation. Dissolution above 80% is desired.

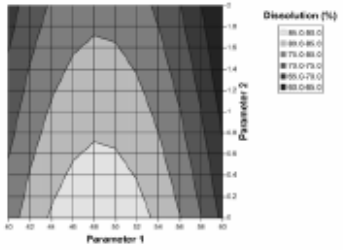



Figure 1b: Contour plot of dissolution from example 1a.

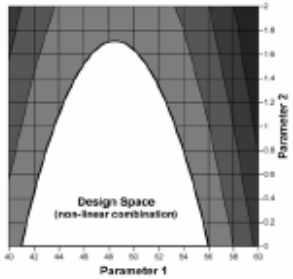



Figure 1c: Design space for granulation parameters, defined by a nonlinear combination of their ranges, that delivers satisfactory dissolution (i.e., >80%).

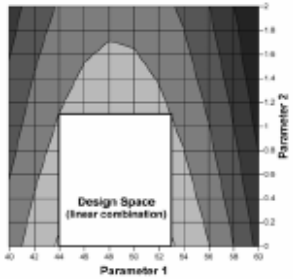


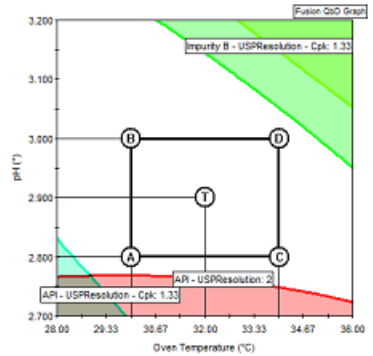

Figure 1d: Design space for granulation parameters, defined by a linear combination of their ranges, that delivers satisfactory dissolution (i.e., >80%).

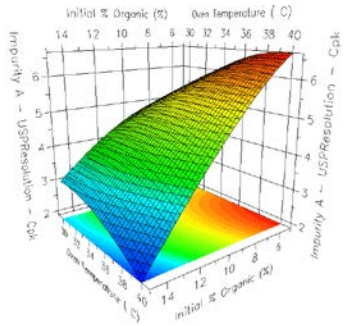
## Fusion QbD

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 |

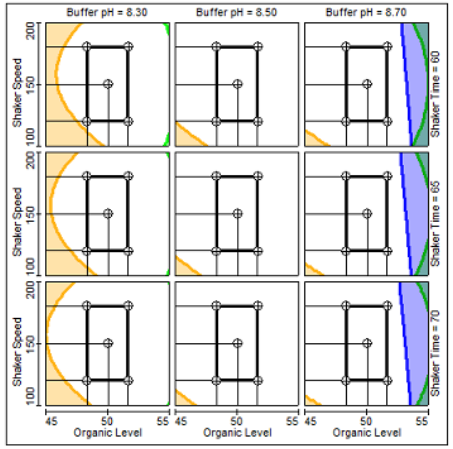
1 of 2

# 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

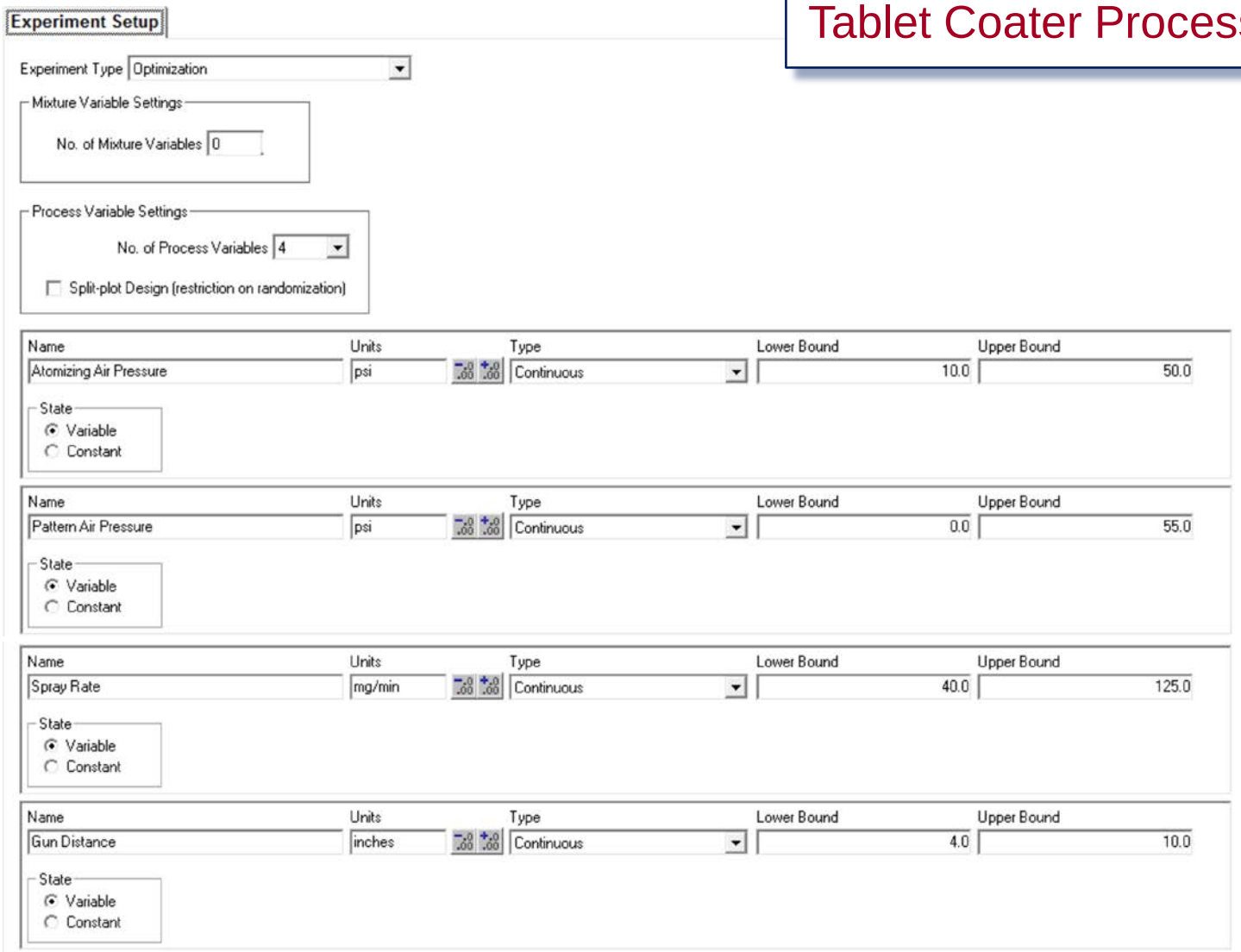
# Example Applications

**Tablet Coating Optimization**

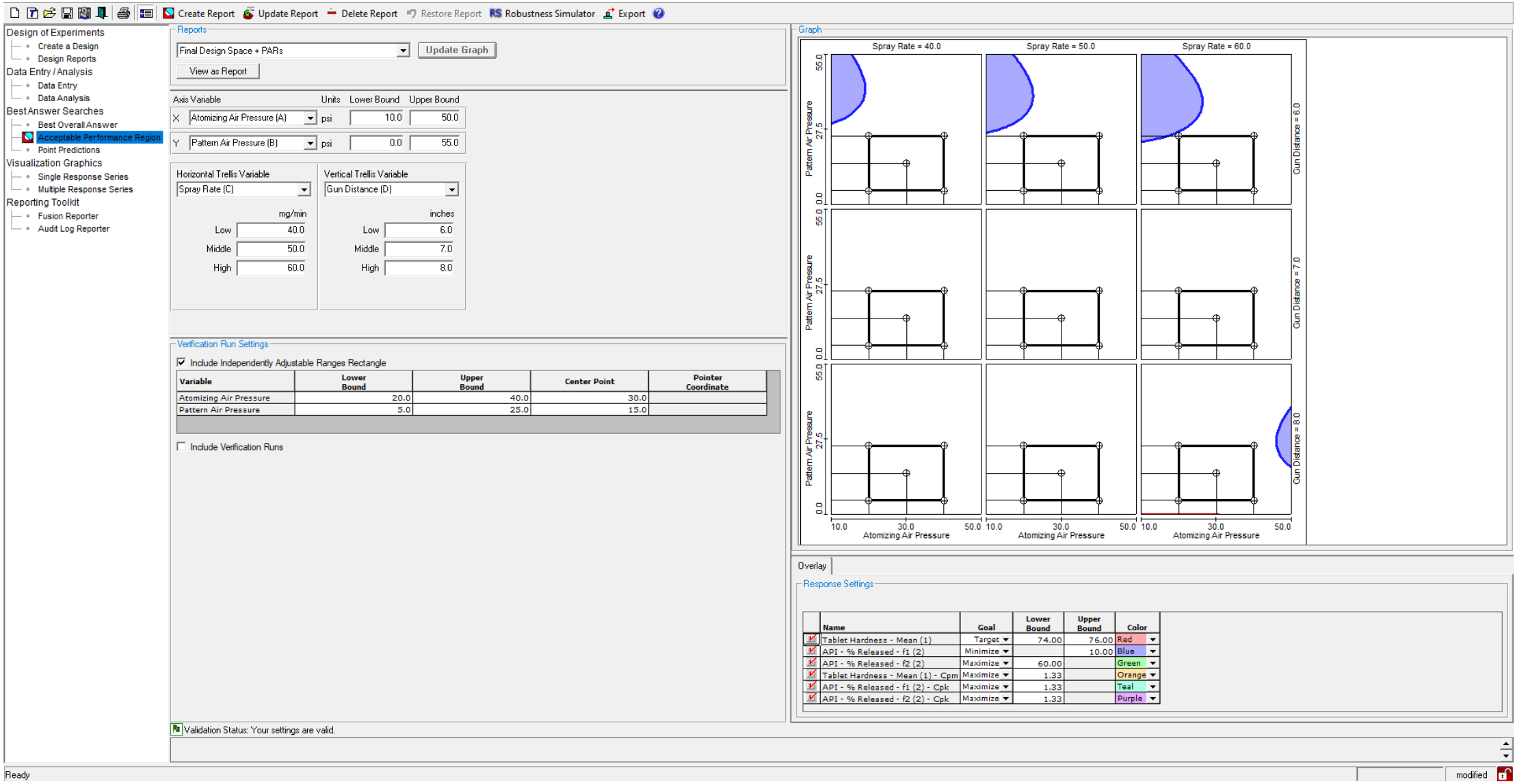
**Tablet Excipient Formulation and Process Optimization**

# Example 1 – Tablet Coater Optimization

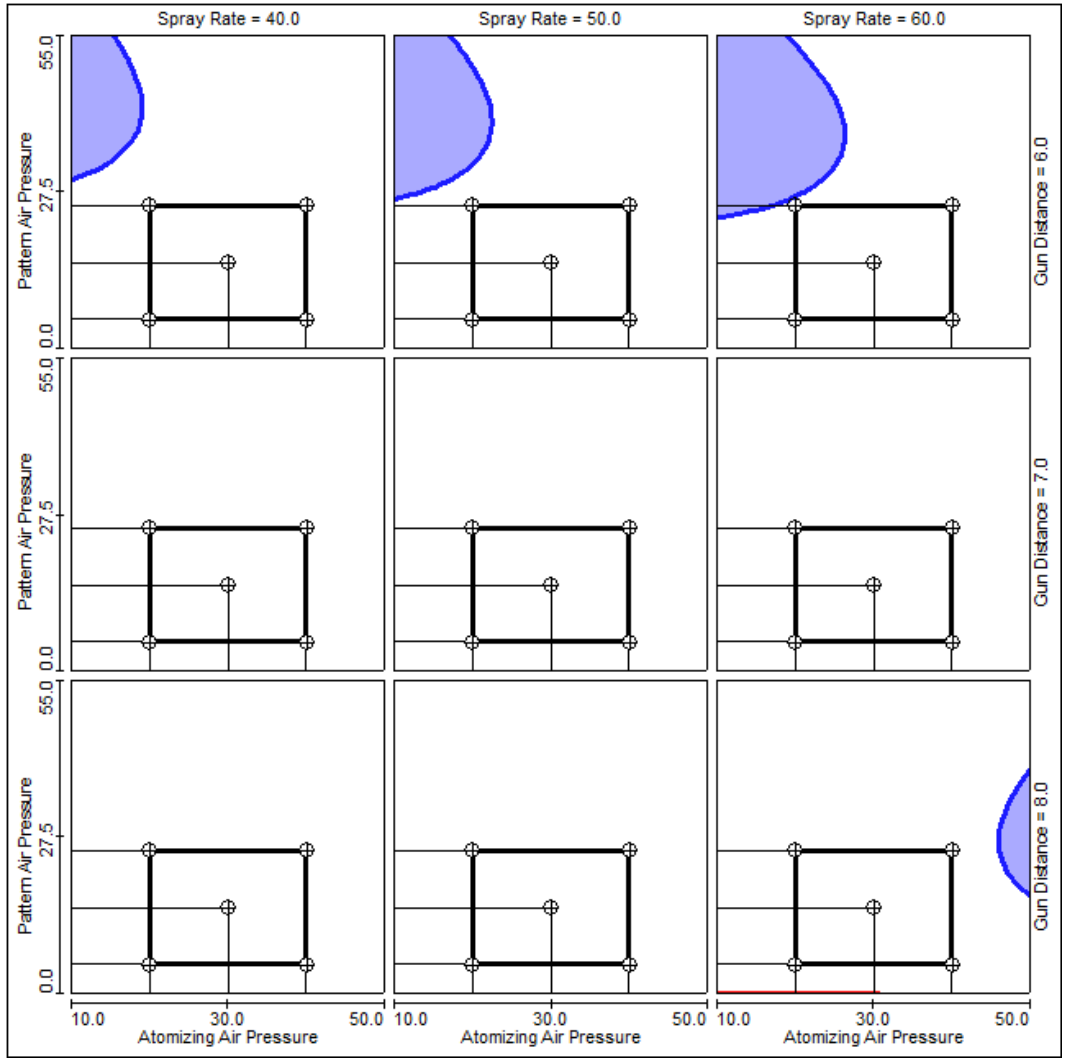
Tablet Coater Processes Optimization Study



# 4-Factor Trellis – Mean Performance and Robustness



# 4-Factor Trellis – Mean Performance and Robustness



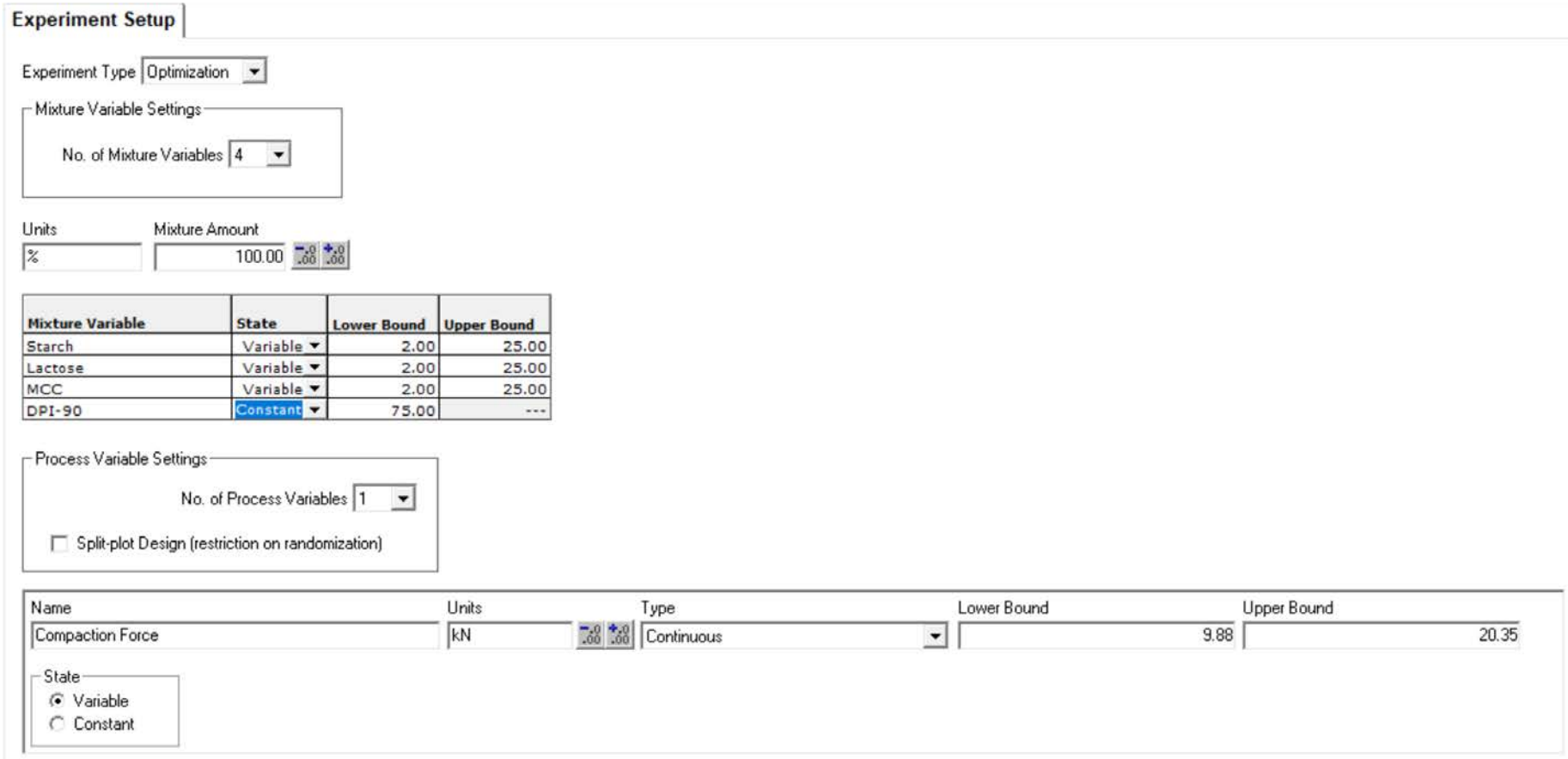

## Independently Adjustable Ranges

| 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 |

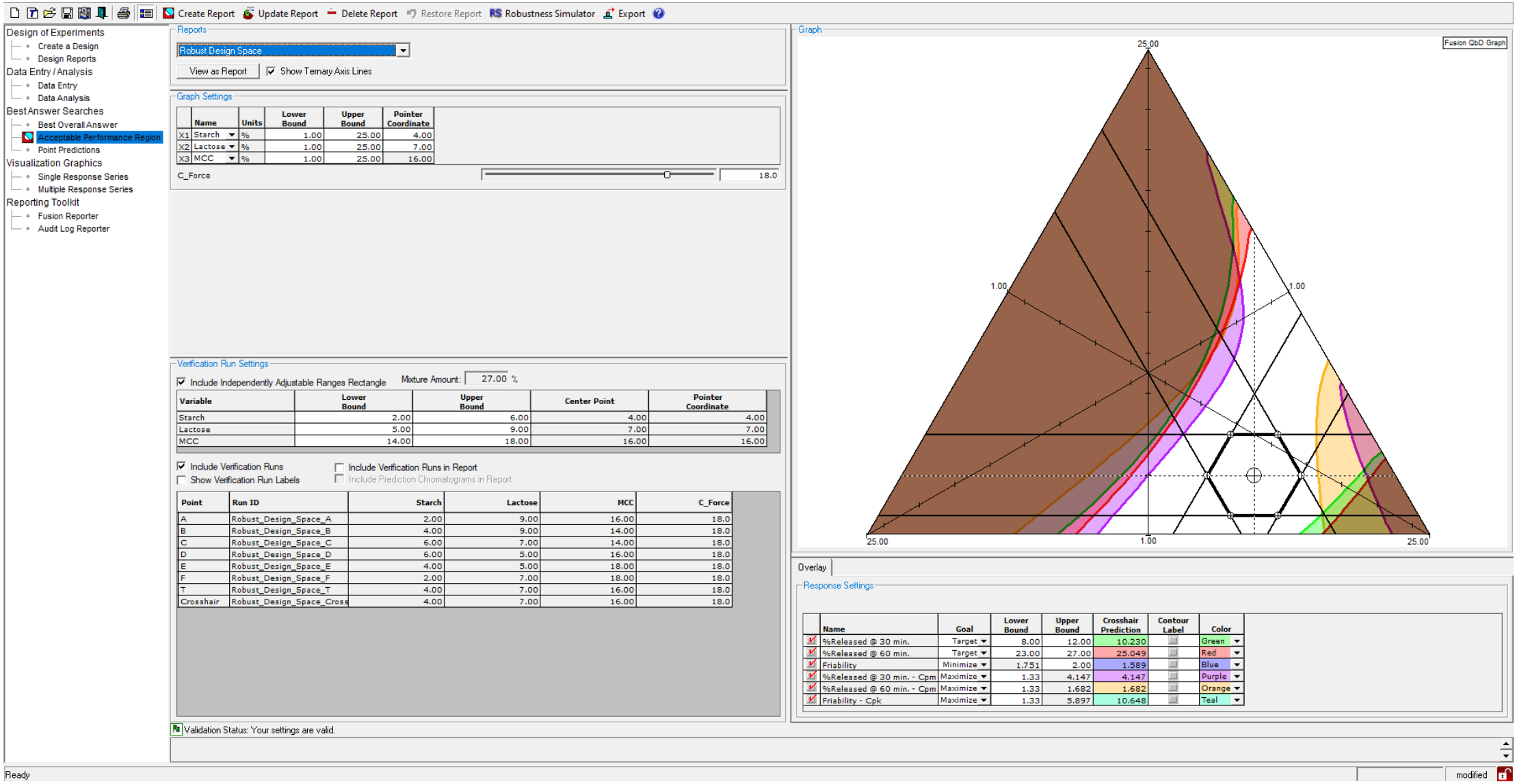
| | | | |
|---|---|---|---|
| Spray Rate | 40 | 60 | 50 |
| Gun Distance | 6 | 8 | 7 |

# Example 2 – Tablet Excipient Formulation and Critical Process Factor Optimization

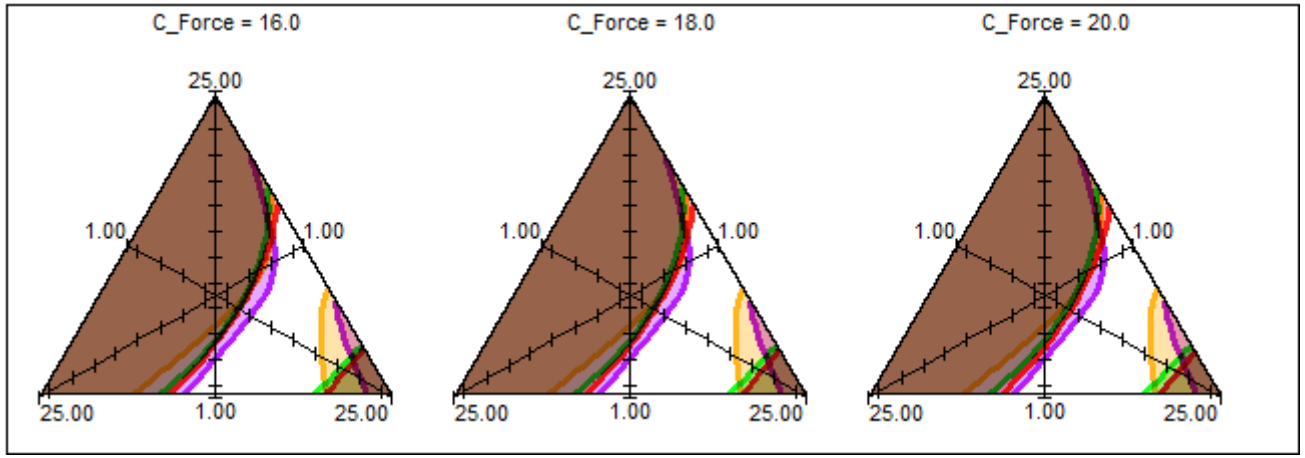
Formulation + Processes Optimization Study



# 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

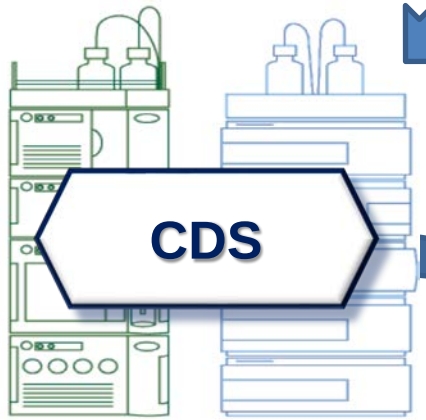
## Sample Prep Expt. Workflow

### 1) Experiment Design

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

### 2) Testing Design

Fusion QbD automatically constructs an LC testing protocol for the Sample Prep Study design as a ready-to-run sequence in the CDS.





### 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 – CE Method Development

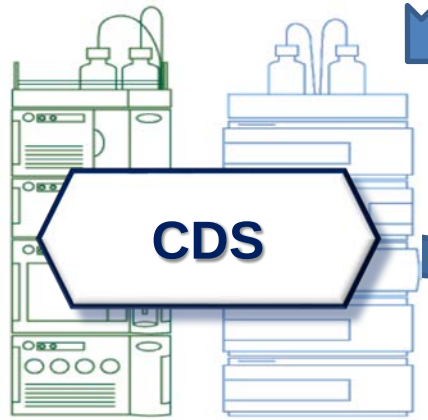
## CE Method Development Expt. Workflow

### 1) Experiment Design

Fusion QbD generates the CE Study design based on the user's variable settings.

### 2) Testing Design

Fusion QbD automatically constructs an LC testing protocol for the CE Study design as a ready-to-run sequence in the CDS.





### 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 CE Study design for automated data modeling.

# FPD – Dissolution Method Development

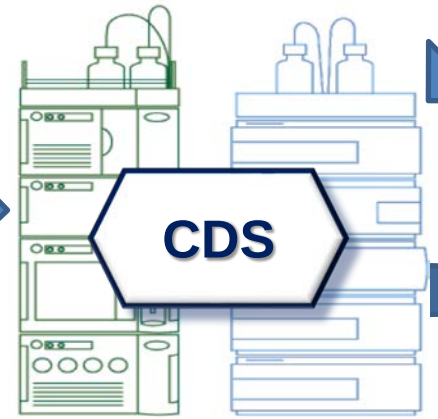
## Dissolution Method Development Expt. Workflow

**1) Experiment Design – e.g.**

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

**2) Testing Design**

Fusion QbD automatically constructs an LC testing protocol for the Dissolution Study design as a ready-to-run sequence in the CDS.





**3) Time Series Testing**

**Dissolution**

**(% Rel. vs Time)**

**4) Results Data Import**

All LC Results for all Compounds

# FPD – Respiratory Drug R&D

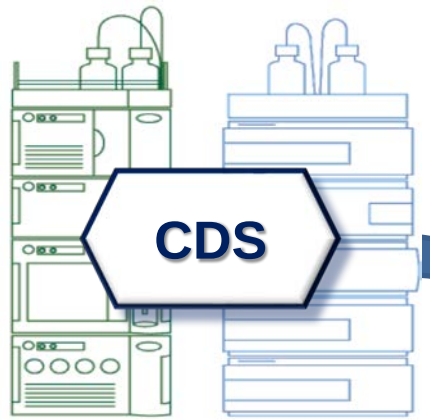
## Respiratory Drug R&D Expt. Workflow

### 1) Experiment Design

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

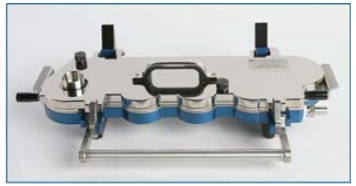
### 2) Testing Design

Fusion QbD automatically constructs an LC Cascade Impaction testing protocol for the R&D study design as a ready-to-run sequence in the CDS.





### 3) Impactor Testing

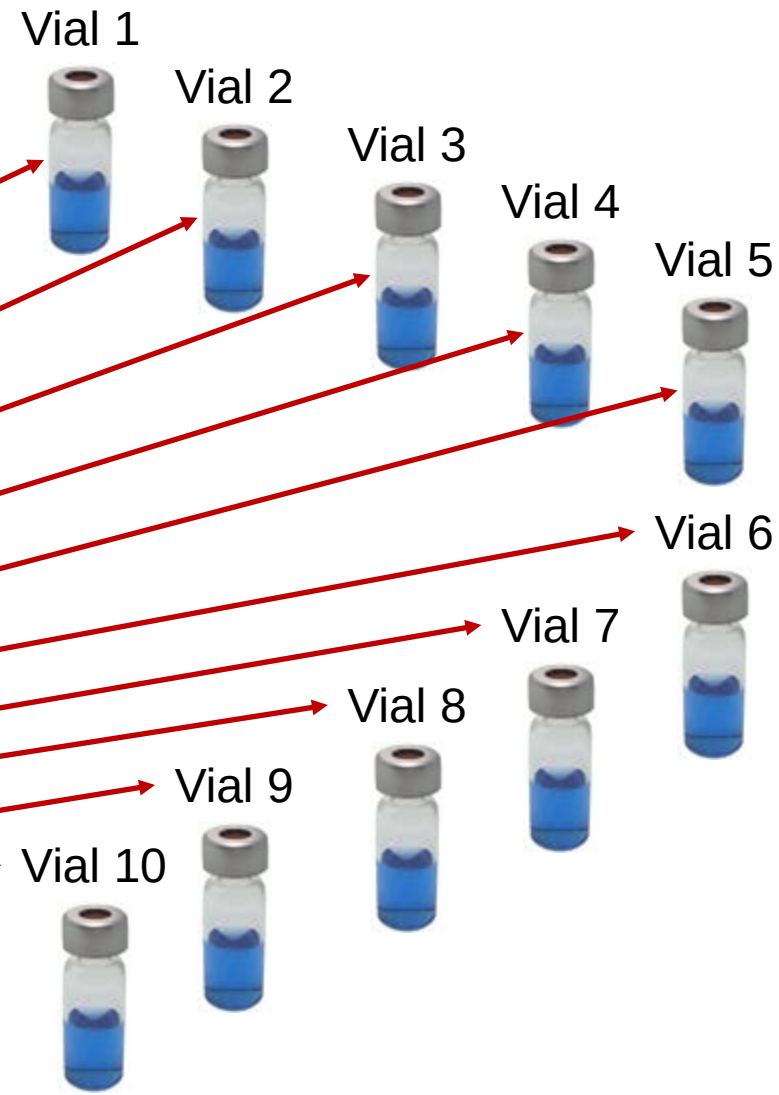


### 4) Results Data Import

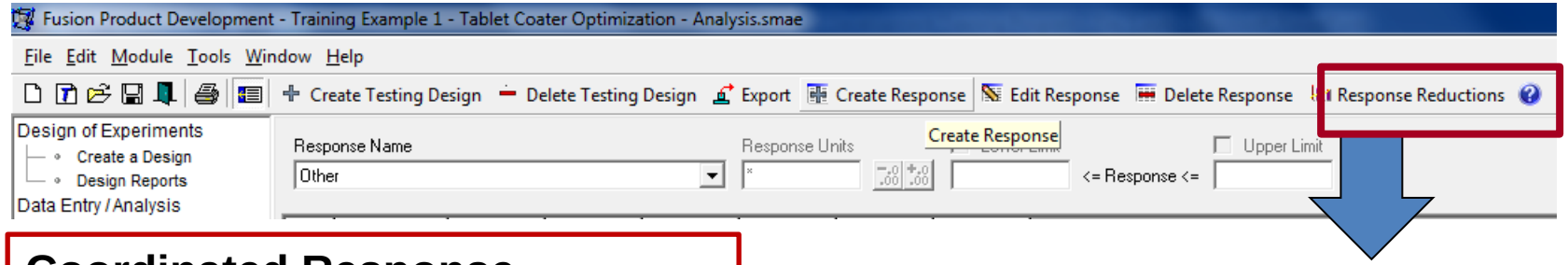
All LC Results for all Compounds

# FPD – Respiratory Drug R&D

## LC Testing Demand for Each Experiment Run

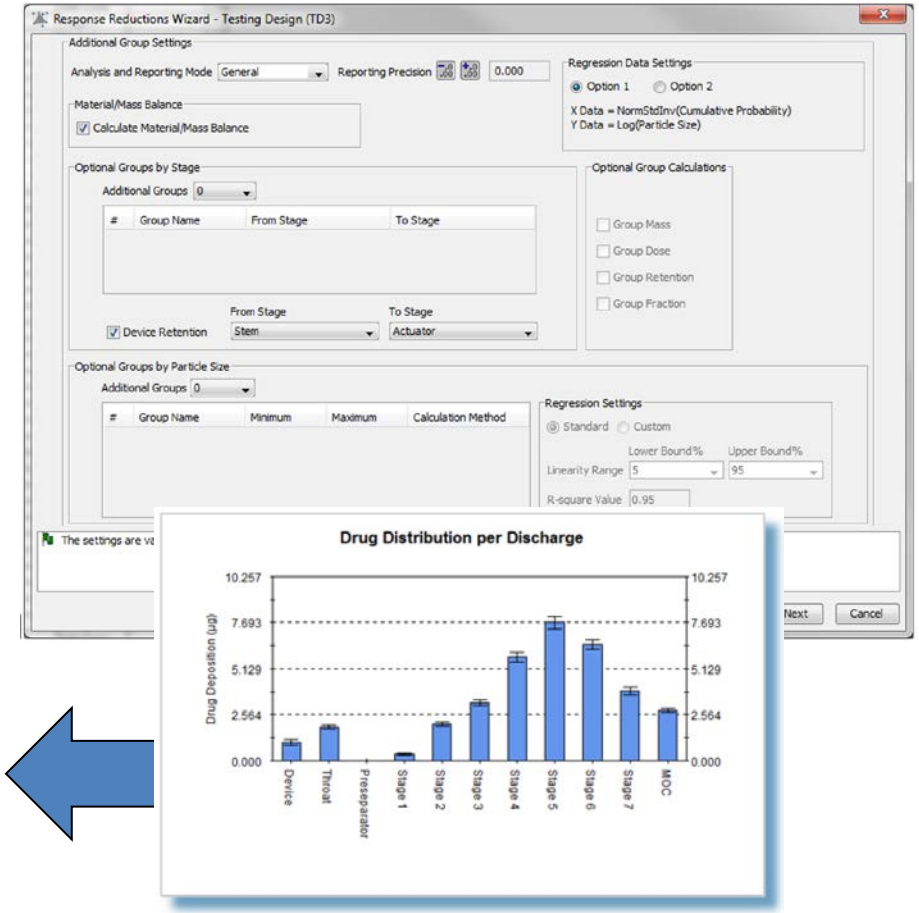


# FPD – Respiratory Drug R&D

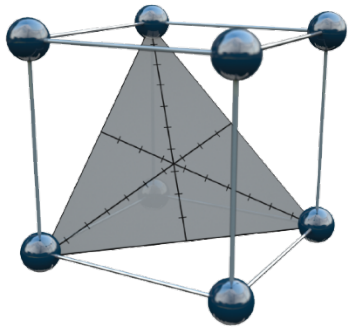



**Coordinated Response Reductions:**

- 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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