



# ***Fusion QbD***

***Fusion Process Development  
For Non-LC Method Development  
Applications***

**S-Matrix Corporation**  
**[www.smatrix.com](http://www.smatrix.com)**

Full Support  
for Part 11  
Compliance



Citrix-Ready  
Certified

## FUSION PROCESS DEVELOPMENT

- Non-LC Method Development – e.g.  
Sample Preparation, Dissolution, GC, CE
- Automated CDS Testing and Data Acquisition

# 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**



**Simplifies Handling of Complex Data**



**Full LC Testing Automation**



**In-silico Monte Carlo Robustness**



**Full QbD Reporting**



**Example Method Development Workflows –**

- **Sample Preparation**
- **Dissolution**
- **GC and CE**

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**Example Method Development Workflows –**

- **Sample Preparation**
- **Dissolution**
- **GC and CE**

# 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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## 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.



## 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.

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

## Why Audit Trail is Important!

Which CDS  
Project did this  
data come from?



Who entered the  
data – was the  
data modified?

Filter Options

Date

Enable

Starting Date:

March 2020						
Sun	Mon	Tue	Wed	Thu	Fri	Sat
23	24	25	26	27	28	29
1	2	3	4	5	6	7
8	9	10	11	12	13	14
15	16	17	18	19	20	21
22	23	24	25	26	27	28
29	30	31	1	2	3	4

Ending Date:

March 2020						
Sun	Mon	Tue	Wed	Thu	Fri	Sat
23	24	25	26	27	28	29
1	2	3	4	5	6	7
8	9	10	11	12	13	14
15	16	17	18	19	20	21
22	23	24	25	26	27	28
29	30	31	1	2	3	4

Users

Enable

Available:

Administrator

Included:

Events

Enable

Available:

- Print Reports
- Experiment Setup
- Enable User Defined Option
- Generate Design
- Export Experiment Design
- Export Testing Design
- Matrix Master Wizard
- Edit Run No. Labels
- Robustness Simulator
- Create Testing Design
- Delete Testing Design
- Response Reductions

Included:

- Import Responses
- Create/Edit Response Data

OK Cancel ?

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Example Method Development Workflows –

- Sample Preparation
- Dissolution
- GC and CE

# Flexible Experiment Design – Easy Setup

**Experiment Setup**

Experiment Type: Optimization

Mixture Variable Settings

No. of Mixture Variables: 4

Units: %      Mixture Amount: 100.00

Mixture Variable	State	Lower Bound	Upper Bound
Starch	Variable	2.00	25.00
Lactose	Variable	2.00	25.00
MCC	Variable	2.00	25.00
DPI-90	Constant	75.00	---

Process Variable Settings

No. of Process Variables: 1

Split-plot Design (restriction on randomization)

Name	Units	Type	Lower Bound	Upper Bound
Compaction Force	kN	Continuous	9.88	20.35

State

Variable  
 Constant

## 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 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

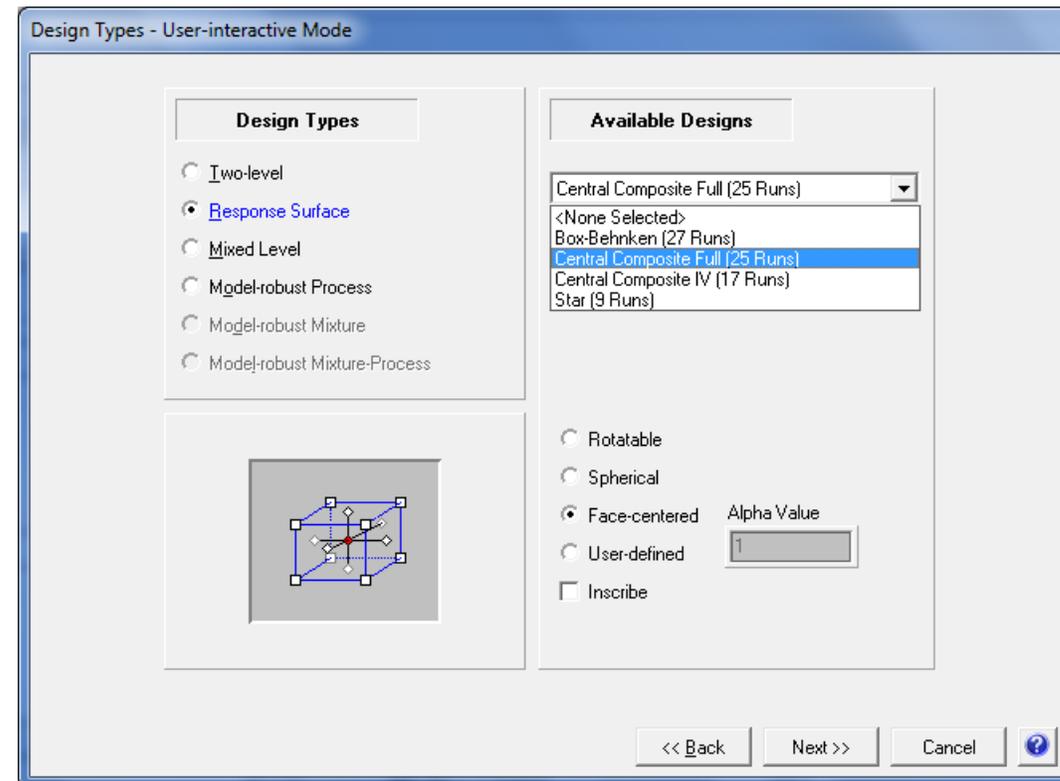
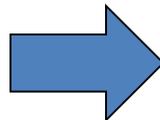
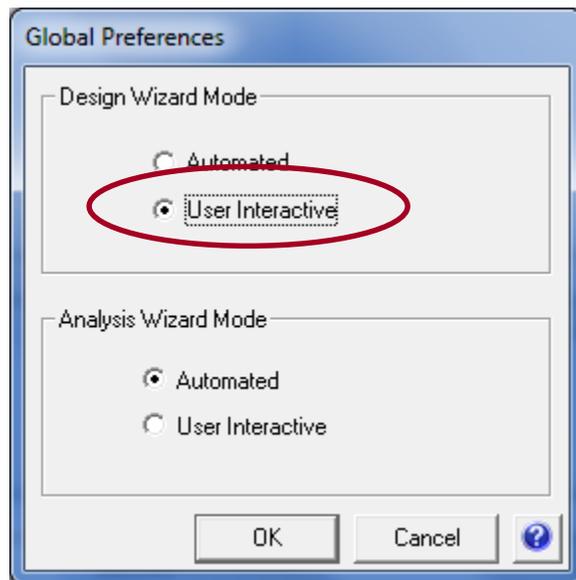
Run No.	Block No.	Atomizing Air Pressure (psi)	Pattern Air Pressure (psi)	Spray Rate (gm/min)	Gun-to-Bed Distance (inches)
1	1	30.0	55.0	82.5	7.0
2	1	30.0	27.5	82.5	10.0
3	1	50.0	0.0	125.0	10.0
4	1	10.0	0.0	40.0	10.0
5	1	10.0	55.0	125.0	10.0
6	1	10.0	55.0	40.0	4.0
7	1	30.0	27.5	82.5	4.0
8	1	30.0	0.0	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



## Can Accept Designs and Results from Other Software

Fusion Product Development - Untitled1

File Edit Activity Tools Window Help

Edit Run No. Labels Matrix Master Create/Edit Response Data Show/Hide Responses Create Testing Design Export Sort Grid

Design of Experiments

- Create a Design
- Design Reports

Data Entry / Analysis

- Data Entry**
- Data Analysis

Best Answer Searches

- Best Overall Answer
- Acceptable Performance Region
- Point Predictions

Visualization Graphics

- Single Response Series
- Multiple Response Series

Reporting Toolkit

- Fusion Reporter
- Audit Log Reporter

	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	3
5	5	0	0	100	100	3
6	6	16.67	66.67	16.66	175	3
7	7	50	0	50	100	3
8	8	50	50	0	200	3
9	9	0	100	0	100	3
10	10	0	100	0	100	3
11	11	100	0	0	100	3
12	12	50	0	50	200	3
13	13	100	0	0	100	3
14	14	66.67	16.67	16.66	175	3
15	15	16.67	66.67	16.66	125	3
16	16	33.33	33.33	33.34	150	1.5

Context Menu:

- Cut
- Copy
- Paste
- Set Response Precision...
- Delete All Responses
- Remove Row
- Redimension Matrix**



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Full 21 CFR Part 11 Compliance Support



Flexible, Automated (1-Click) Design and Analysis



**Simplifies Handling of Complex Data**



Full LC Testing Automation



In-silico Monte Carlo Robustness



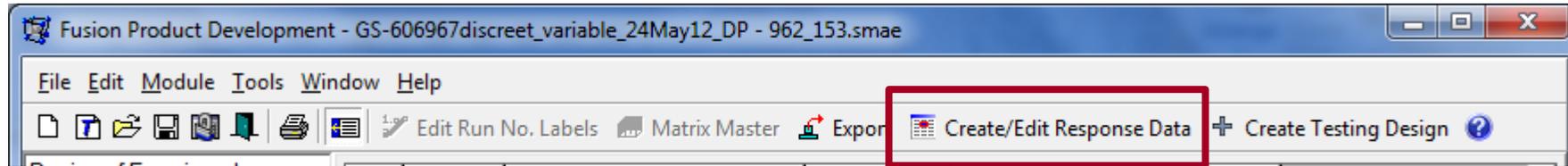
Full QbD Reporting



Example Method Development Workflows –

- Sample Preparation
- Dissolution
- GC and CE

# Simple Data Entry – One Test Result Per Trial



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

Create/Edit Response Data

Response Name: Example Response    Response Units: Units    Lower Limit: 0    Upper Limit: 100

0 <= Response <= 100

Run No.	Example Response
1	
2	
3	
4	
5	
6	
7	
8	
9	
10	
11	
12	
13	
14	
15	
16	
17	
18	
19	
20	
21	
22	

Add following to empty cells: 0    Update

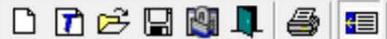
Validation Status: Your settings are valid.

New    Delete    OK    Close    Apply    ?

# Simple Data Entry – One Test Result Per Trial

Fusion Product Development - Temporary File.smae

File Edit Activity Tools Window Help


 Edit Run No. Labels  Matrix Master  Create/Edit Response Data  Show/Hide

Design of Experiments

- Create a Design
- Design Reports

Data Entry / Analysis

- Data Entry**
- Data Analysis

Best Answer Searches

- Best Overall Answer
- Acceptable Performance Region
- Point Predictions

Visualization Graphics

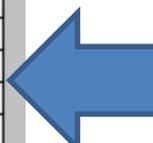
- Single Response Series
- Multiple Response Series

Reporting Toolkit

- Fusion Reporter
- Audit Log Reporter

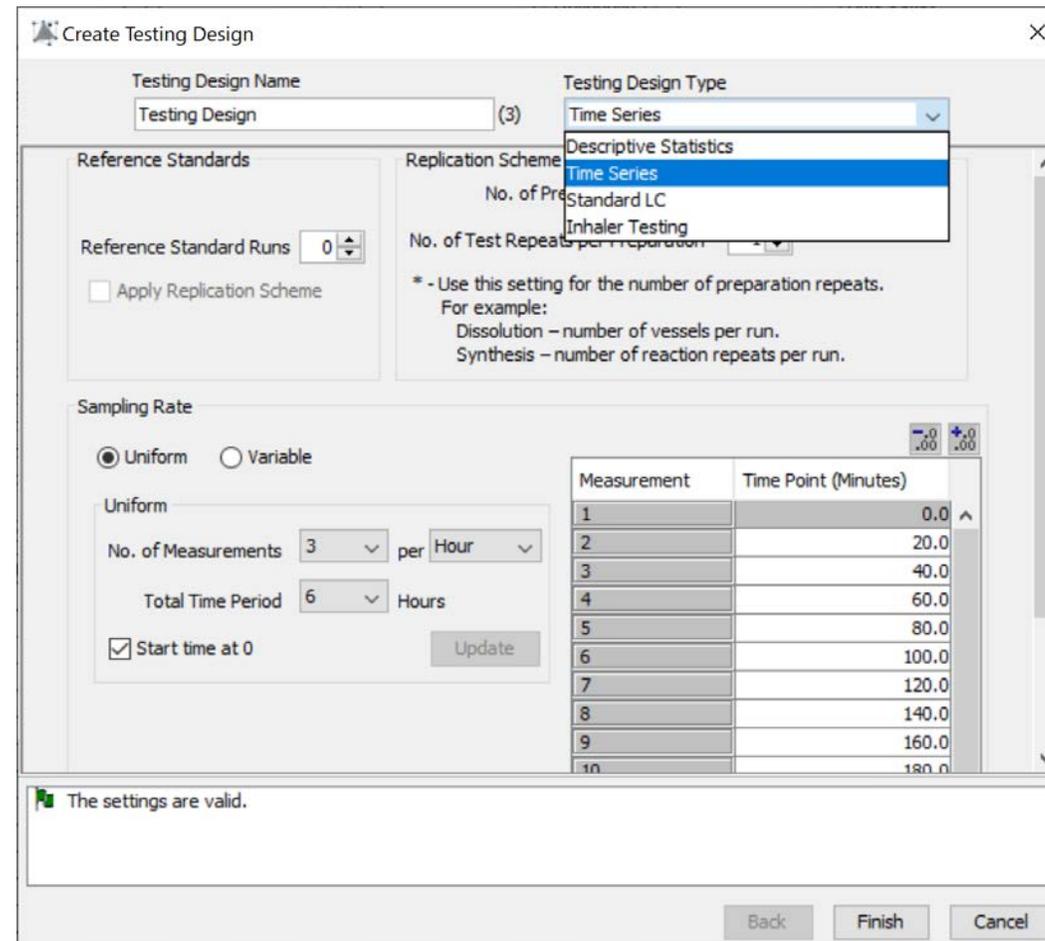
	Run No.	Starch	Lactose	MCC	C_Force	Example Response
1	1	11.5	2	11.5	20.35	
2	2	2	11.5	11.5	15.12	
3	3	2	21	2	15.12	
4	4	2	2	21	20.35	
5	5	2	11.5	11.5	20.35	
6	6	5.17	14.67	5.16	17.73	
7	7	2	2	21	15.12	
8	8	2	2	21	9.88	
9	9	21	2	2	9.88	
10	10	11.5	11.5	2	15.12	
11	11	21	2	2	9.88	
12	12	5.17	5.17	14.66	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



## RDH Handles Complex Data Simply and Easily!

- Multiple test results per run.
- Time Series – testing at multiple time points per run.



Testing Design Name: Testing Design (3)

Testing Design Type: Time Series

Reference Standards: Reference Standard Runs: 0

Apply Replication Scheme:

Replication Scheme: No. of Preparation Repeats: 1

No. of Test Repeats per Preparation: 1

\* - Use this setting for the number of preparation repeats. For example:  
Dissolution – number of vessels per run.  
Synthesis – number of reaction repeats per run.

Sampling Rate:  Uniform  Variable

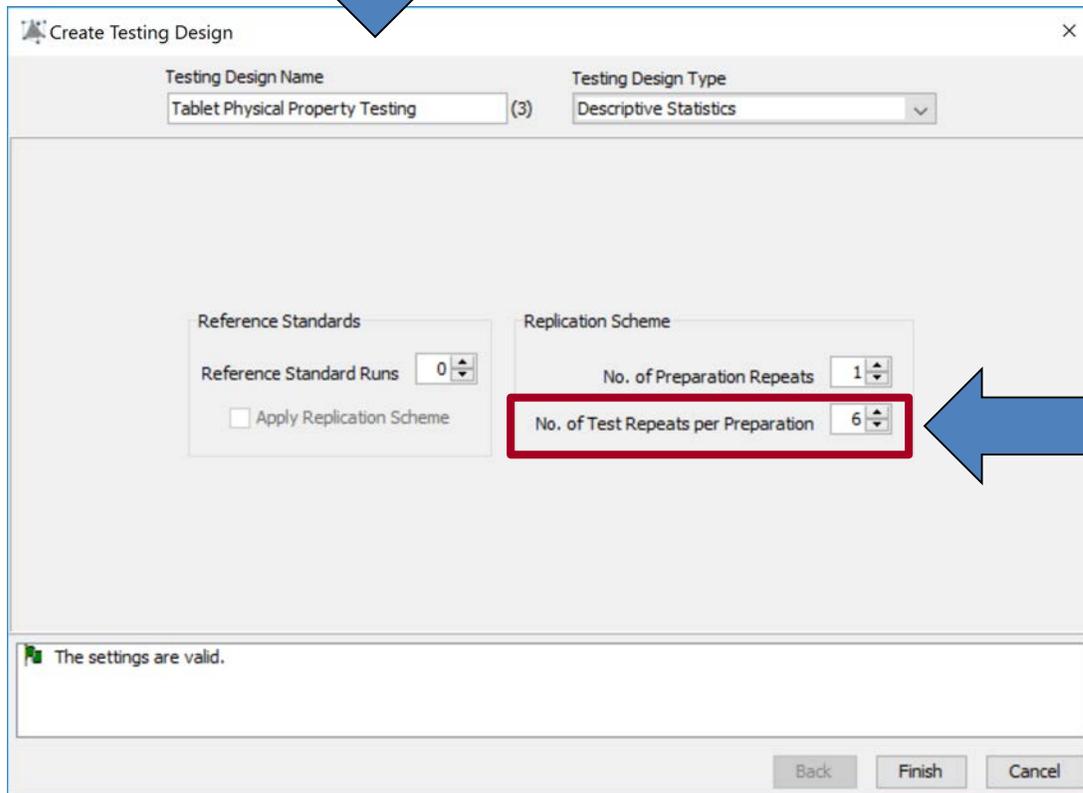
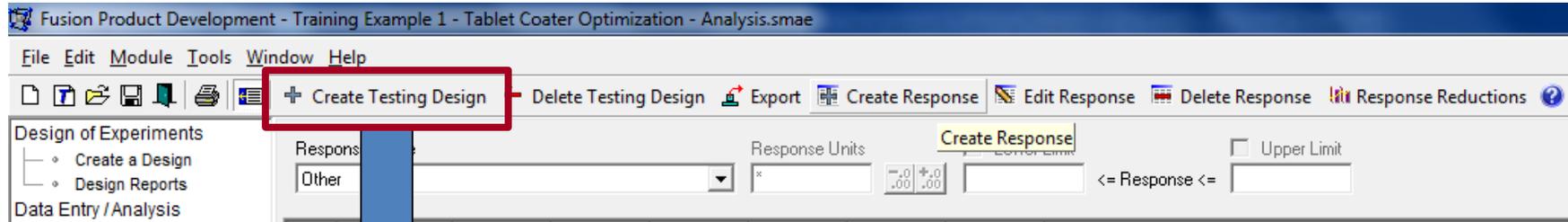
Uniform: No. of Measurements: 3 per Hour. Total Time Period: 6 Hours.  Start time at 0. Update

Measurement	Time Point (Minutes)
1	0.0
2	20.0
3	40.0
4	60.0
5	80.0
6	100.0
7	120.0
8	140.0
9	160.0
10	180.0

The settings are valid.

Buttons: Back, Finish, Cancel

# RDH – Multiple Test Results Per Trial



## Example Protocol –

Test six (6) tablets for LC and Non-LC measurements:

- % Released
- Hardness
- Friability
- Gloss
- ...

# RDH – Multiple Test Results Per Trial

Fusion Product Development - Training Example 1 - Tablet Coater Optimization - Analysis.smae

File Edit Module Tools Window Help

 Create Testing Design
  Delete Testing Design
  Export
  **Create Response**
 Edit Response
  Delete Response
  Response Reductions

Design of Experiments

- Create a Design
- Design Reports

Data Entry / Analysis

Response Name: Other    Response Units: \*     Lower Limit     Upper Limit

<= Response <=

Response Name: 60 Deg. Gloss    Response Units: \*     Lower Limit     Upper Limit    Testing Design Type: Descriptive Statistics    View Testing Design

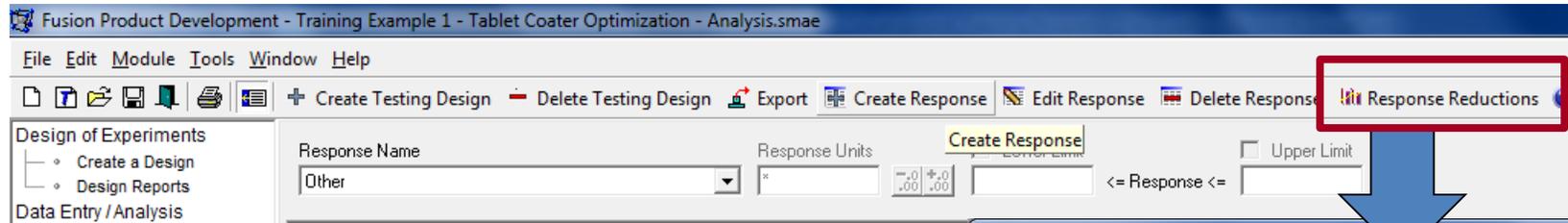
None Selected

Hardness

		E T4	F T5	G T6
1	1			
2	2			
3	3			
4	4			
5	5			
6	6			
7	7			
8	8			
9	9			
10	10			
11	11			
12	12			
13	13			
14	14			
15	15			
16	16			
17	17			
18	18			
19	19			
20	20			
21	21			
22	22			
23	23			
24	24			
25	25			
26	26			
27	27			
28	28			

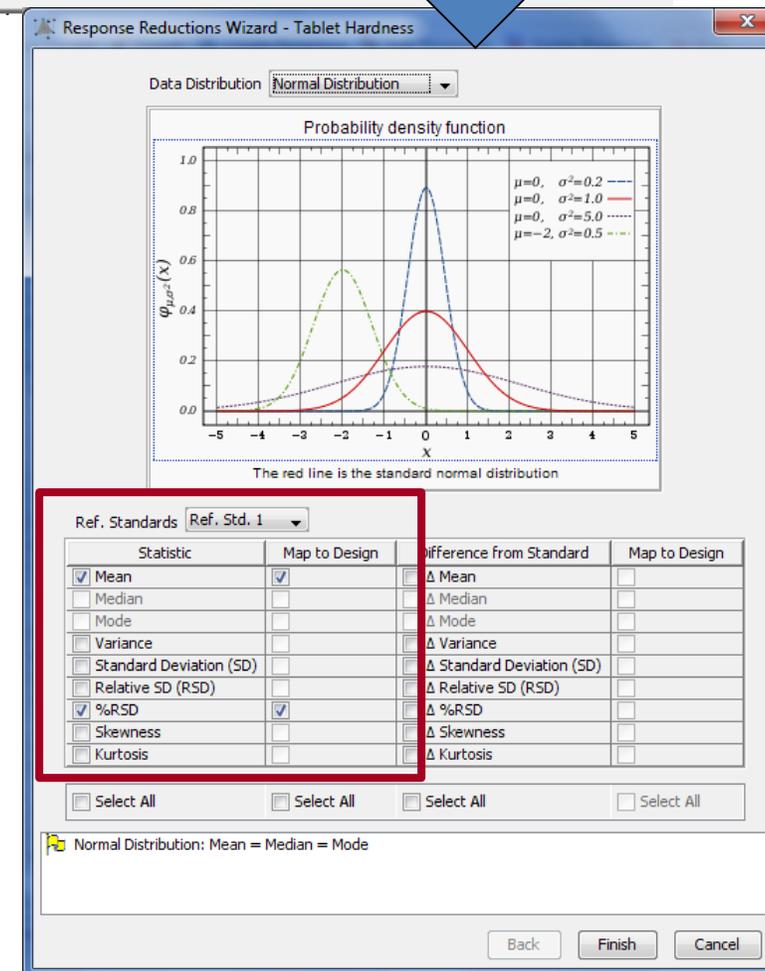
Testing Design is a template – automatically replicate the template to import/enter multiple responses with same testing protocol.

# RDH – Multiple Test Results Per Trial



## Automated Response Reductions:

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



# RDH – Multiple Test Results Per Trial

Fusion Product Development - Tablet Formulation and Process Optimization - New Analysis - 990.smae

File Edit Activity Tools Window Help

Edit Run No. Labels Matrix Master Create/Edit Response Data

Design of Experiments

- Create a Design
- Design Reports

Data Entry / Analysis

- Data Entry**
- Data Analysis

Best Answer Searches

- Best Overall Answer
- Acceptable Performance Region
- Point Predictions

Visualization Graphics

- Single Response Series
- Multiple Response Series

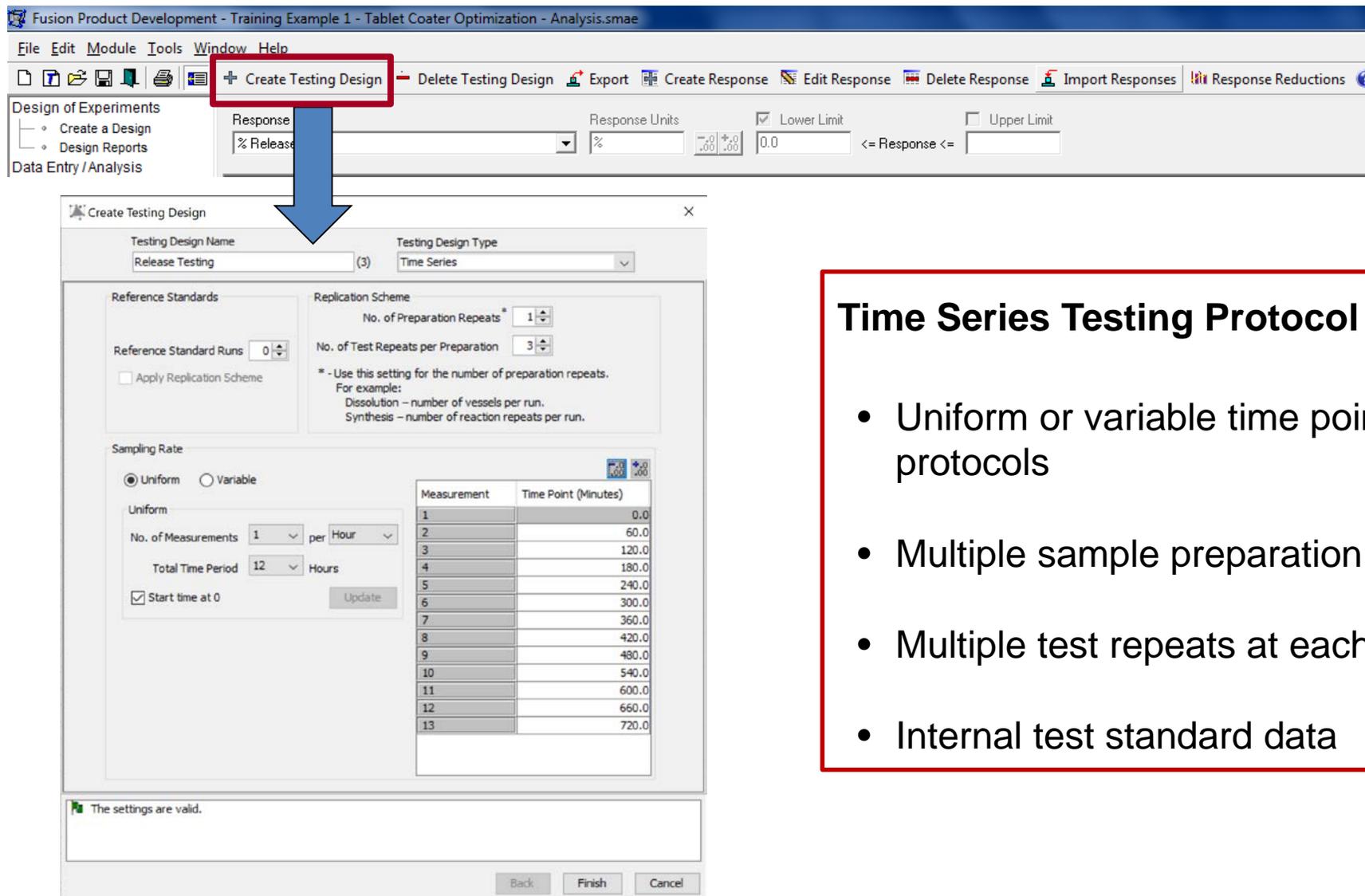
Reporting Toolkit

- Fusion Reporter
- Audit Log Reporter

	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

RDH Wizard automatically calculates results from test replicates for each run and maps the results to the design for automated analysis and modeling

# RDH – Testing at Multiple Time Points Per Trial



The screenshot shows the 'Create Testing Design' dialog box in the Fusion Product Development software. The 'Testing Design Name' is 'Release Testing' and the 'Testing Design Type' is 'Time Series'. The 'Reference Standards' section has 'Reference Standard Runs' set to 0. The 'Replication Scheme' section has 'No. of Preparation Repeats' set to 1 and 'No. of Test Repeats per Preparation' set to 3. The 'Sampling Rate' is set to 'Uniform' with 'No. of Measurements' set to 1 per 'Hour' over a 'Total Time Period' of 12 hours. The 'Start time at 0' checkbox is checked. A table shows 13 measurement time points from 0.0 to 720.0 minutes. The 'The settings are valid.' message is displayed at the bottom.

Measurement	Time Point (Minutes)
1	0.0
2	60.0
3	120.0
4	180.0
5	240.0
6	300.0
7	360.0
8	420.0
9	480.0
10	540.0
11	600.0
12	660.0
13	720.0

## Time Series 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 Design Template

Fusion Product Development - Fusion Product Development Tutorial - Part 2 - 990 SR2b.smae

File Edit Activity Tools Window Help

Response Name: 
 Response Units: 
 Lower Limit
  Upper Limit
 Testing Design Type:

	A	B	C	D	E	F	G	H	I	J	K	L	M	N
	Run No.	t - 0.00	t - 60.00	t - 120.00	t - 180.00	t - 240.00	t - 300.00	t - 360.00	t - 420.00	t - 480.00	t - 540.00	t - 600.00	t - 660.00	t - 720.00
1	1.a													
2	1.b													
3	1.c													
4	2.a													
5	2.b													
6	2.c													
7	3.a													
8	3.b													
9	3.c													
10	4.a													
11	4.b													
12	4.c													
13	5.a													
14	5.b													
15	5.c													
16	6.a													
17	6.b													
18	6.c													
19	7.a													
20	7.b													
21	7.c													
22	8.a													
23	8.b													
24	8.c													
25	9.a													

Testing Design is a template –  
 The template is automatically replicated to support auto-import of all your desired results for all compounds from the CDS.

# RDH –Testing at Multiple Time Points Per Trial

Fusion Product Development - Fusion Product Development Tutorial - Part 2 - 990 SR2b.smae

File Edit Activity Tools Window Help

Create Testing Design 
  Delete Testing Design 
  Create Response 
  Edit Response 
  Delete Response 
  Response Reductions 
  Export 
  Import Responses

Design of Experiments  
 • Create a Design  
 • Design Reports

Data Entry / Analysis  
 Data Entry  
 • Data Analysis

Best Answer Searches  
 • Best Overall Answer  
 • Acceptable Performance Region  
 • Point Predictions

Visualization Graphics  
 • Single Response Series  
 • Multiple Response Series

Reporting Toolkit  
 • Fusion Reporter  
 • Audit Log Reporter

Response Name: API - % Released  
 Response Units: %  
 Lower Limit  
 Upper Limit  
 Testing Design Type: Time Series

	A Run No.	B t - 0.00	C t - 60.00	D t - 120.00	E t - 180.00	F t - 240.00	G t - 300.00	H t - 360.00	I t - 420.00
1	1.a	0.00	13.40	21.35	29.55	35.50	41.45	46.50	51.50
2	1.b	0.00	13.60	21.55	29.65	35.45	41.45	46.45	51.50
3	1.c	0.00	13.50	21.60	29.30	35.55	41.60	46.55	51.35
4	2.a	0.00	12.20	24.65	36.70	45.95	53.65	60.65	65.55
5	2.b	0.00	12.15	24.80	36.35	46.25	53.35	60.50	65.45
6	2.c	0.00	12.25	25.25	36.45	46.10	53.50	60.35	65.50
7	3.a	0.00	8.60	10.55	14.45	17.25	21.65	25.05	28.60
8	3.b	0.00	8.45	10.10	14.20	17.05	21.80	25.00	28.75
9	3.c	0.00	8.45	10.55	14.25	17.30	21.95	25.25	28.75
10	4.a	0.00	11.50	21.05	30.70	38.00	44.55	50.30	56.80
11	4.b	0.00	11.40	21.15	30.30	38.25	44.50	50.00	56.80
12	4.c	0.00	11.30	21.10	30.50	38.05	44.45	50.00	56.80
13	5.a	0.00	10.95	21.50	31.05	38.65	46.25	52.00	58.20
14	5.b	0.00	10.85	21.70	31.00	39.15	46.50	52.10	58.10
15	5.c	0.00	10.90	21.40	30.95	38.90	46.15	52.20	58.00

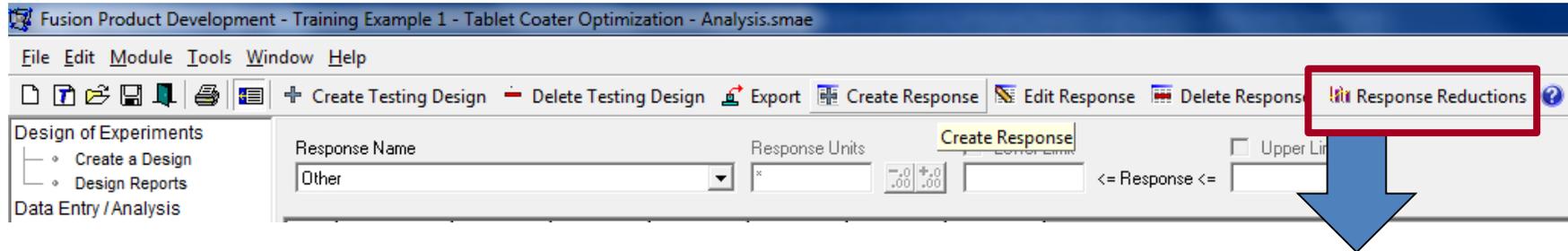
Imported Replicate Run Data

	A Run No.	B t - 0.00	C t - 60.00	D t - 120.00	E t - 180.00	F t - 240.00	G t - 300.00	H t - 360.00	I t - 420.00	J t - 480.00
1	1	0.00	13.50	21.50	29.50	35.50	41.50	46.50	51.50	55.50
2	2	0.00	12.20	24.90	36.50	46.10	53.50	60.50	65.50	70.90
3	3	0.00	8.50	10.40	14.30	17.20	21.80	25.10	28.70	32.70
4	4	0.00	11.40	21.10	30.50	38.10	44.50	50.10	56.80	62.40
5	5	0.00	10.90	21.50	31.00	38.90	46.30	52.10	58.10	63.50
6	6	0.00	10.90	21.50	31.00	38.90	46.30	52.10	58.10	63.50
7	7	0.00	10.90	21.50	31.00	38.90	46.30	52.10	58.10	63.50
8	8	0.00	10.90	21.50	31.00	38.90	46.30	52.10	58.10	63.50
9	9	0.00	10.90	21.50	31.00	38.90	46.30	52.10	58.10	63.50
10	10	0.00	10.90	21.50	31.00	38.90	46.30	52.10	58.10	63.50
11	11	0.00	10.90	21.50	31.00	38.90	46.30	52.10	58.10	63.50
12	12	0.00	10.90	21.50	31.00	38.90	46.30	52.10	58.10	63.50
13	13	0.00	10.90	21.50	31.00	38.90	46.30	52.10	58.10	63.50
14	14	0.00	10.90	21.50	31.00	38.90	46.30	52.10	58.10	63.50

Auto-averaged Data

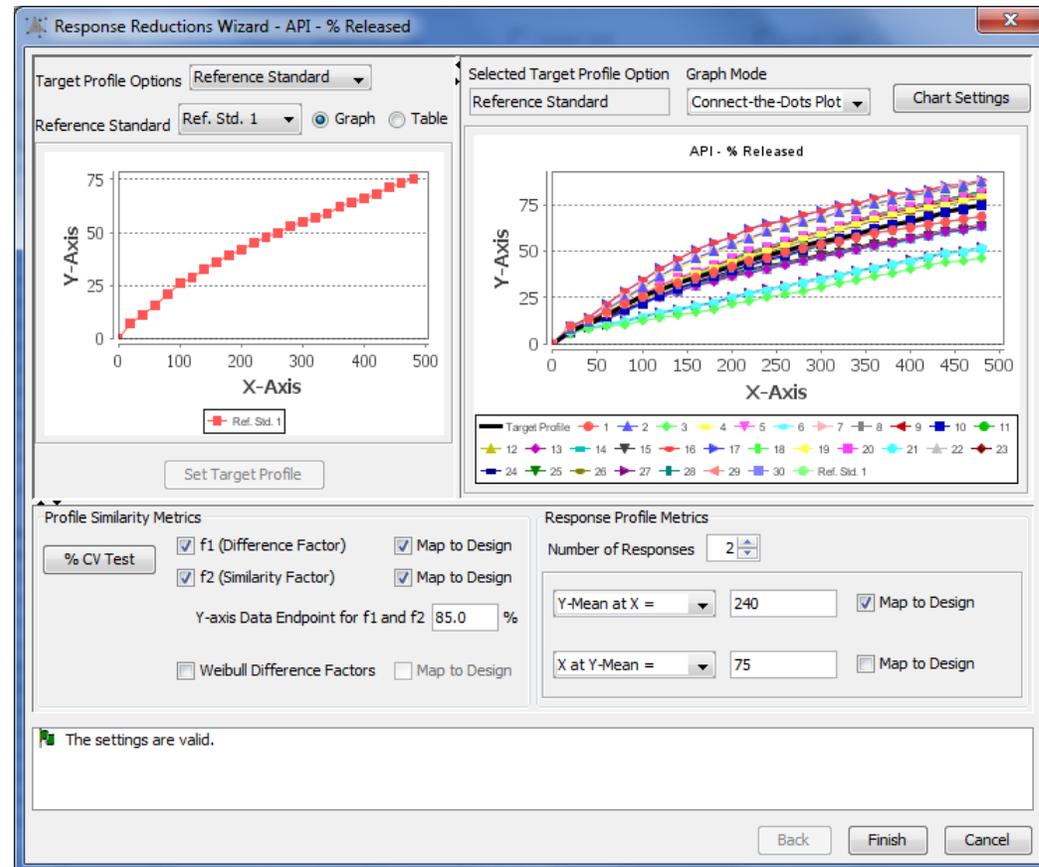
FPD Automatically Generates  
 Average Response Curves (Profiles)  
 from Individual Test Repeats for each  
 Run. For example, results from  
 multiple dissolution vessels.

# RDH –Testing at Multiple Time Points Per Trial



## Coordinated Response Reductions:

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



# RDH –Testing at Multiple Time Points Per Trial

Fusion Product Development - Fusion Product Development Tutorial - Part 2 - 990 SR2b.smae

File Edit Activity Tools Window Help


















Design of Experiments

- Create a Design
- Design Reports
- Data Entry / Analysis
  - Data Entry**
  - Data Analysis
- Best Answer Searches
  - Best Overall Answer
  - Acceptable Performance Region
  - Point Predictions
- Visualization Graphics
  - Single Response Series
  - Multiple Response Series
- Reporting Toolkit
  - Fusion Reporter
  - Audit Log Reporter

	Run No.	Atomizing Air Pressure	Pattern Air Pressure	Spray Rate	Gun Distance	Tablet Hardness - Mean (1)	API - % Released - f1	API - % Released - f2
1	1	30	55	82.5	7	75.18	4.73	76.05
2	2	30	27.5	82.5	10	75.07	22.00	48.33
3	3	50	0	125	10	77.15	42.89	34.03
4	4	10	0	40	10	76.23	6.64	71.73
5	5	10	55	125	10	75.65	9.26	65.27
6	6	10	55	40	4	75.76	34.22	38.91
7	7	30	27.5	82.5	4	74.24	22.38	48.01
8	8	30	0	82.5	7	75.91	4.83	75.68
9	9	50	55	40	10	74.63	7.95	68.85
10	10	50	0	40	4	75.52	2.91	85.02
11	11	30	27.5	82.5	7	74.52	9.40	64.50
12	12	10	55	40	10	74.62	1.28	95.72
13	13	10	0	125	4	74.38	14.40	56.80
14	14	50	55	40	4	75.89	14.50	56.63
15	15	10	0	40	4	75.43	13.27	58.13
16	16	10	0	125	10	77.25	28.44	43.31
17	17	50	55	125	10	75.54	28.63	43.18
18	18	50	27.5	82.5	7	74.68	8.58	66.38
19	19	50	0	40	10	76.06	19.98	50.12
20	20	30	27.5	82.5	7	74.77	8.58	66.38
21	21	10	55	125	4	74.76	36.39	37.63
22	22	50	55	125	4	74.81	13.36	58.18
23	23	10	0	40	4	75.43	11.73	60.35
24	24	10	27.5	82.5	7	74.68	9.26	64.83
25	25	30	27.5	82.5	7	74.70	9.12	65.16
26	26	30	27.5	40	7	74.70	5.04	76.17
27	27	10	55	40	4	75.94	34.54	38.74
28	28	50	0	125	4	74.39	3.47	83.17
29	29	50	0	40	4	75.46	3.13	84.20
30	30	30	27.5	125	7	74.59	14.08	57.19

RDH Wizard automatically maps calculated results to the design for analysis and modeling

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Simplifies Handling of Complex Data



**Full LC Testing Automation**



In-silico Monte Carlo Robustness



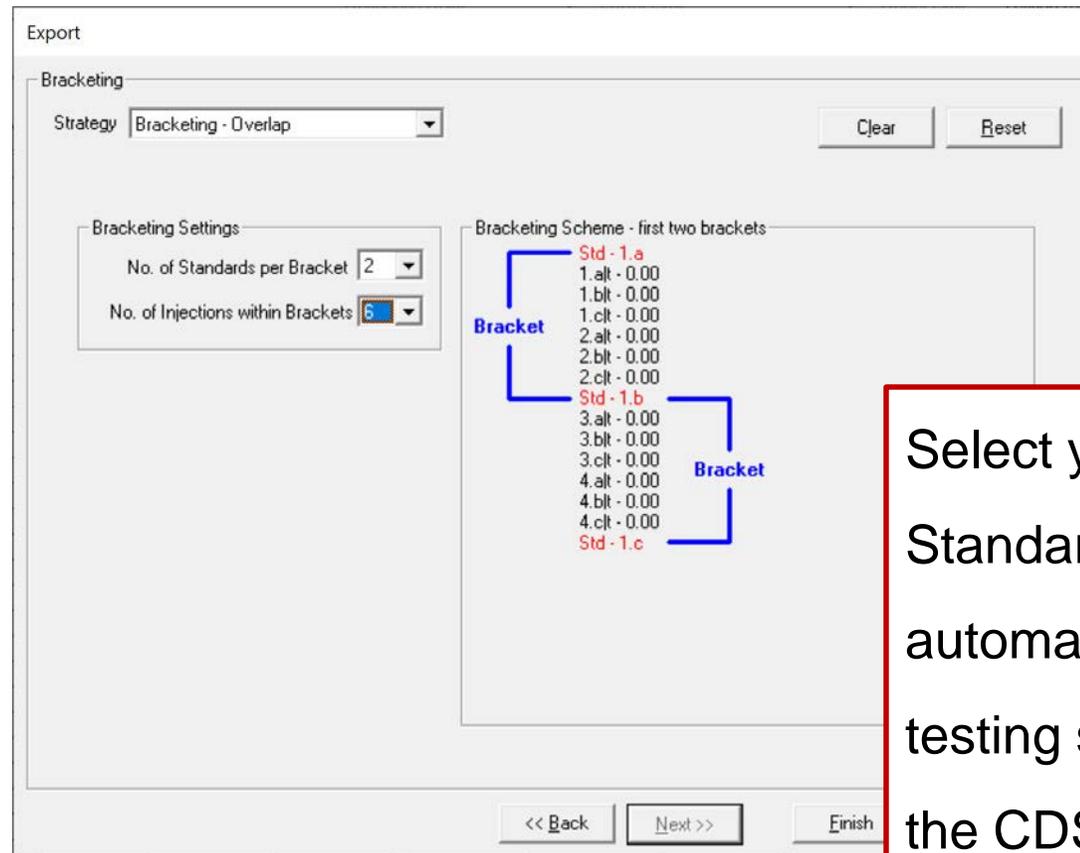
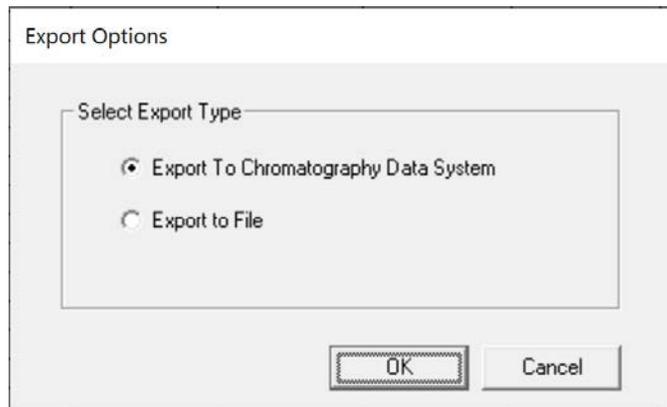
Full QbD Reporting



Example Method Development Workflows –

- Sample Preparation
- Dissolution
- GC and CE

## Automatically Builds your Standards Protocol into the Exported Testing Design Sequence



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

# Import All Required Results Data from the CDS

Select a Project and Result Set

Select Project

- Customers
- Distributors
- S-Matrix
  - ADL
  - FIT
  - FMD Tutorial - 9\_9\_0
    - RD1 - Screen - 9\_9\_0
    - RD2 - 9\_9\_0 - Named Peaks
    - RD2 - Optimization - 9\_9\_0
  - FMV - A\_L\_R
  - Internal Development
  - RD1 - Demo Screening Expt
  - RD2 - Demo Optimization Expt
  - Test
  - Tip of the Week

Select Result Set(s)

Result Set Name	ResultSetID	Date	Sample Set
RD2 Optimization Named	8941	6/9/2019 1:47:33 PM PDT	RD2 Optimizati
RD2 Optimization Named	6323	2/11/2019 9:30:14 AM EST	RD2 Optimizati

Select Processed Channel:  
PDA Ch1 225nm@4.8nm, Time offset by: 0.020 mins

Fetch Selected Result Sets

Result(s) for Import

Sample	ResultID	Date	Type	Channel ID
1	9168	6/9/2019 2:19:15 PM	LC	6321
10	9150	6/9/2019 2:10:17 PM	LC	6404
11	9148	6/9/2019 2:09:35 PM	LC	6412
12	9146	6/9/2019 2:08:44 PM	LC	6420
13	9144	6/9/2019 2:08:10 PM	LC	6428
14	9142	6/9/2019 2:07:30 PM	LC	6436
15	9140	6/9/2019 2:06:40 PM	LC	6444
16	9138	6/9/2019 2:06:04 PM	LC	6452

PeakTracker Data Import

Select Raw PDA Channel: None Selected | Select Raw MS Channel: None Selected | MS Time Offset (min): 0.000

Spectra Extraction Points: Leading (%) 30.00 | Trailing (%) 30.00 | Threshold Setting: MS Intensity 0

Select Processed MS Channel: [ ] Track Non-absorbing Peaks

User Types (logged in as 'Owner'): Owner

Ready

Next >> | Cancel | ?

Automatically import any desired results data from the CDS for any compounds.

Named Compounds in CDS

Available

Included

- A
- API
- B
- D
- D-Deg
- E
- F
- G

Response Data

IMPORTANT:  
Do not select any Resolution responses if you intend to use the Rs-Map Response.

Available

Included

- USPNoise
- USPResolution
- USPResolutionAtHH
- Width
- WidthAt10Pct
- WidthAt13\_4Pct
- WidthAt32\_4Pct
- WidthAt4\_4Pct

Auto-imported Responses... | << Back | Next >> | Cancel | ?



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Full LC Testing Automation



**In-silico Monte Carlo Robustness**



Full QbD Reporting



Example Method Development Workflows –

- Sample Preparation
- Dissolution
- GC and CE

## 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.

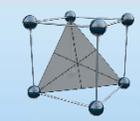
### 3. Process Capability

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  $C_p = C_{pk}$ .

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

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



Fully Automated  
In-silico  
Monte Carlo  
Robustness  
Simulation

**Robustness Simulator**

Use  $C_{pk}$  when one of the two cases below applies to the response.

- The response goal is **Maximize**, there is an absolute **Lower** specification limit, and at least some predicted response values **are** near the absolute lower limit.
- The response goal is **Minimize**, there is an absolute **Upper** specification limit, and at least some predicted response values **are** near the absolute upper limit.

**Note:**

- $C_{pl}$  is computed when only a lower specification is entered.
- $C_{pu}$  is computed when only an upper specification is entered.

**$C_{pk}$  – Lower or Upper Specification Limit**

$$C_{pk} = \min(C_{pl}, C_{pu}) \quad \text{where} \quad C_{pl} = \frac{\bar{x} - LSL}{3\sigma} \quad \text{and} \quad C_{pu} = \frac{USL - \bar{x}}{3\sigma}$$

**LSL or USL:**  
The numerical distance from the mean performance result to the specification limit.

**Lower Limit Example**

**Response Settings**

Include Additional Error

Model Error    External Error   C.I. for Simulation: 1 Sigma

Enabled	Response	Robustness Index	Specification Limit Delta (±)	LSL	USL	Target	Additional Error	Additional Error Amount (±1σ Value)
<input checked="" type="checkbox"/>	Tablet Hardness...	%RSD						
<input checked="" type="checkbox"/>	API - % Release...	Cpk				10.000		
<input checked="" type="checkbox"/>	API - % Release...	Cpk		60.000				

Select All   Select None

The settings are valid.

Back   Finish   Cancel

**Built-in Robustness Metrics – Simply:**

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

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Full LC Testing Automation ✓

In-silico Monte Carlo Robustness ✓

**Full QbD Reporting** ✓

Example Method Development Workflows –

- Sample Preparation
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## 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.)

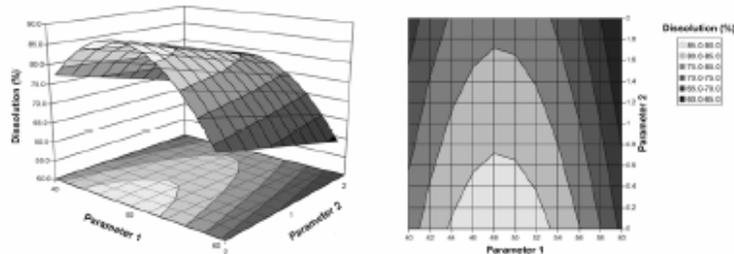


Figure 1a: Response surface plot of dissolution as a function of two parameters of a granulation operation. Dissolution above 80% is desired.

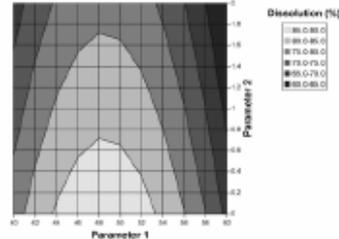


Figure 1b: Contour plot of dissolution from example 1a.

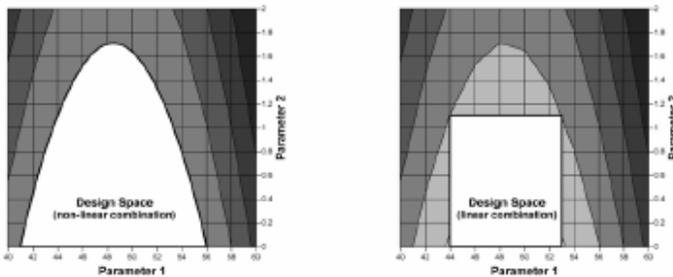


Figure 1c: Design space for granulation parameters, defined by a nonlinear combination of their ranges, that delivers satisfactory dissolution (i.e., >80%).

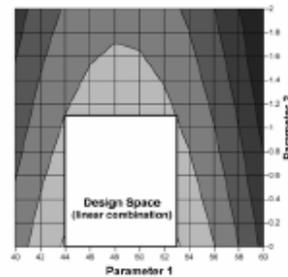


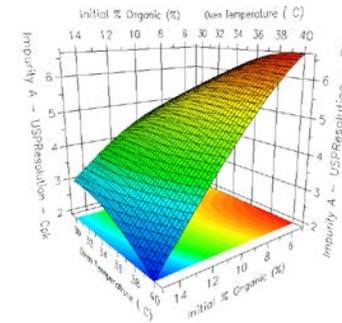
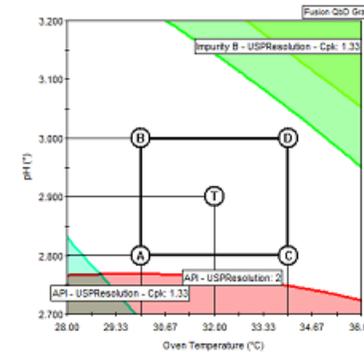
Figure 1d: Design space for granulation parameters, defined by a linear combination of their ranges, that delivers satisfactory dissolution (i.e., >80%).

## Fusion QbD

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



### 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	2.48
Impurity A - USPResolution	(*)	Maximize	2.00		Blue	3.88
Impurity B - USPResolution	(*)	Maximize	2.00		Green	2.39
API - USP Tailing	(*)	Target	0.90	1.10	Orange	1.01
API - USPResolution - Cpk	(*)	Maximize	1.33		Teal	3.88
Impurity A - USPResolution - Cpk	(*)	Maximize	1.33		Purple	6.44
Impurity B - USPResolution - Cpk	(*)	Maximize	1.33		Light	4.88
API - USP Tailing - Cpm	(*)	Maximize	1.33		Sky	5.40

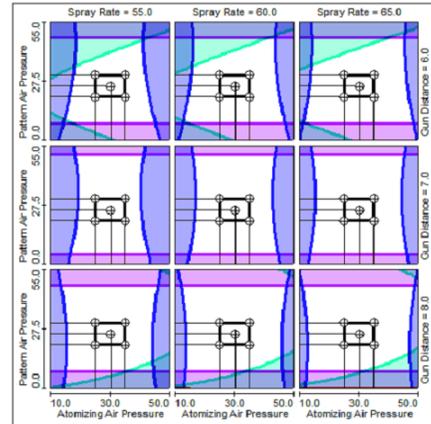
### Graph Variable Settings

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

Name: [USER\_NAME]  
 Company: S-Matrix Corporation  
 Project: Project1  
 Date: 22-APR-2015-18:38:42-PDT [UTC-07:00]



Trellis--D.S. +-PARs



**Proven-Acceptable-Range-Settings**

Axis	Name	Units	Lower Bound	Upper Bound	Centerpoint
X	Atomizing Air Pressure		25	35	30
Y	Pattern Air Pressure		20	30	25

**Trellis-Variable-Settings**

Series	Variable Name	Units	Low	Middle	High
Horizontal	Spray Rate		55	60	65
Vertical	Gun Distance		6	7	8

**Response-Variable-Goals**

Name	Units	Goal	Color	Lower Bound	Upper Bound
Tablet Hardness* Mean (TD1)			Red	74.0	76.0
Tablet Hardness* %RSD (TD1)			Blue		5.0
API* %Released* I1 (TD2)			Green		15.0
API* %Released* I2 (TD2)			Orange	50.0	
API* %Released* I1 (TD2)* Cp			Teal	2.0	
API* %Released* I2 (TD2)* Cp			Purple	2.0	

**Graph-Variable-Goals**

Name	Units	Graph Setting	Range/Level(s)
Atomizing Air Pressure		X Axis Variable	10.0 <= Atomizing Air Pressure <= 50.0
Pattern Air Pressure		Y Axis Variable	0.0 <= Pattern Air Pressure <= 55.0
Spray Rate		Horizontal Trellis Levels	55.0, 60.0, 65.0
Gun Distance		Vertical Trellis Levels	6.0, 7.0, 8.0

**Experiment-Variables-for-Robustness-Simulator**

Included	Variable Name	Units	Maximum Expected Variation (+/- 3 Sigma Value)
Yes	Atomizing Air Pressure	psi	5.0
Yes	Pattern Air Pressure	psi	5.0
Yes	Spray Rate	mg/min	2.0
Yes	Gun Distance	inches	1.0

**Responses-for-Robustness-Simulator**

[RESPONSE_NAME_COLUMN_HEAD R]	Specification Limit (+/- distance from target)	Robustness Index	LSL	USL	Target	Additional Error	Additional Error Amount (+/- 3 Sigma Value)
[RESPONSE_NAME]0003		--	--	--	--		None
[RESPONSE_NAME]0004		--	--	--	--		None

**Report Settings**

Setting	Value
Report Name	--
Action	Report Created
Report Type	Trellis Graph
Graph Category	Process
Include PARs	True
Include Verification Runs	False
Include Verification Runs In Report	False

Reports can be output in a variety of file formats:

PDF / MS Word / HTML / TXT / XLSX

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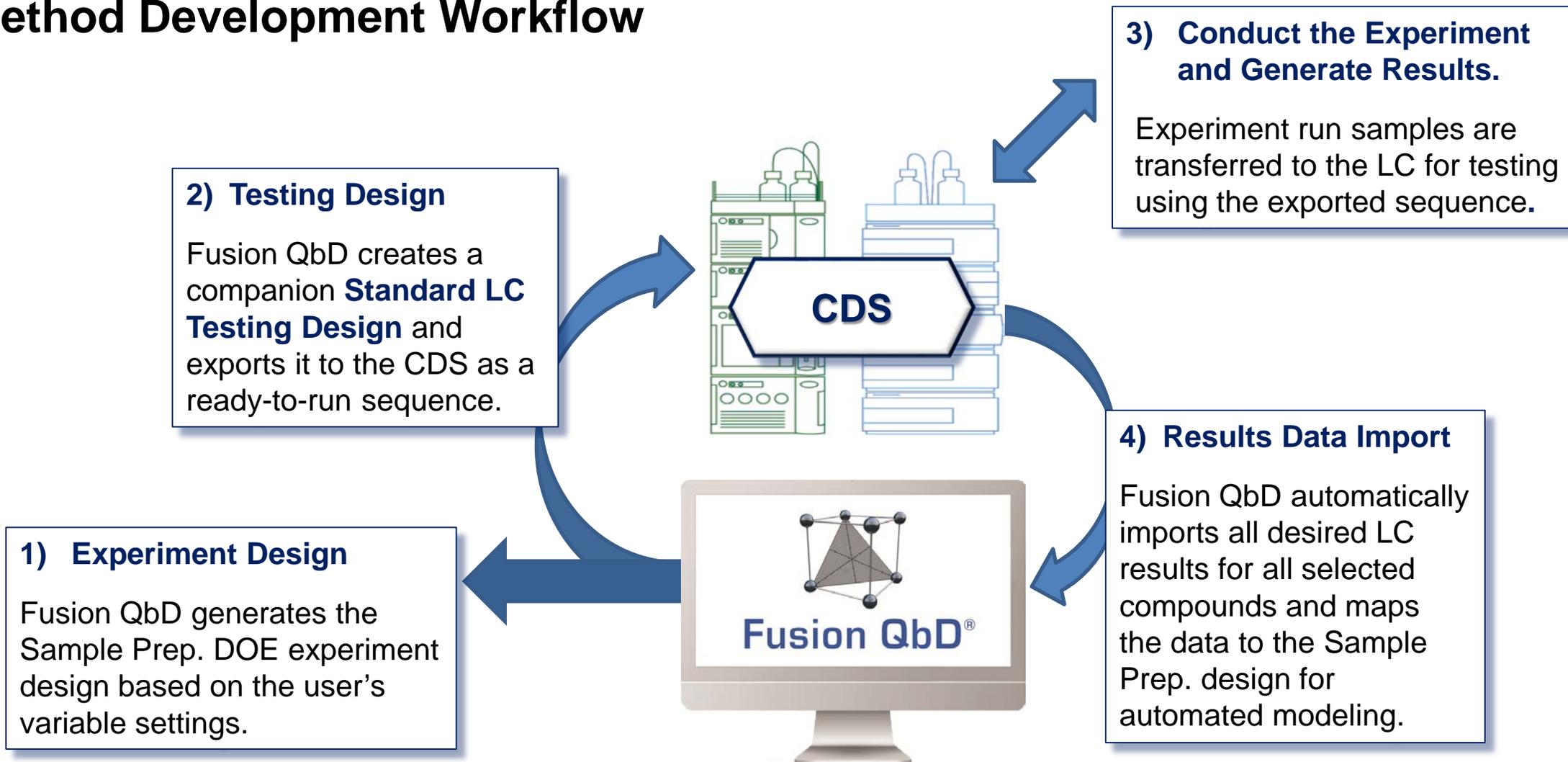
Full QbD Reporting



## Example Method Development Workflows –

- **Sample Preparation**
- **Dissolution**
- **GC and CE**

## Method Development Workflow



## Dissolution R&D Workflow

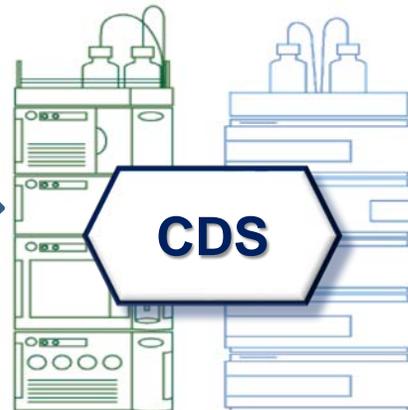
### 1) Experiment Design

Fusion QbD generates the Dissolution DOE experiment design based on the user's variable settings:

- Process Variables – e.g.
  - Time, Temp, Speed, ...
- Chemistry Variables – e.g.
  - Buffer  $\Delta$ C, pH, ...

### 2) Testing Design

Fusion QbD creates a companion **Time Series Testing Design** and exports it to the CDS as a ready-to-run sequence.



### 3) Conduct the Experiment and Generate Results.



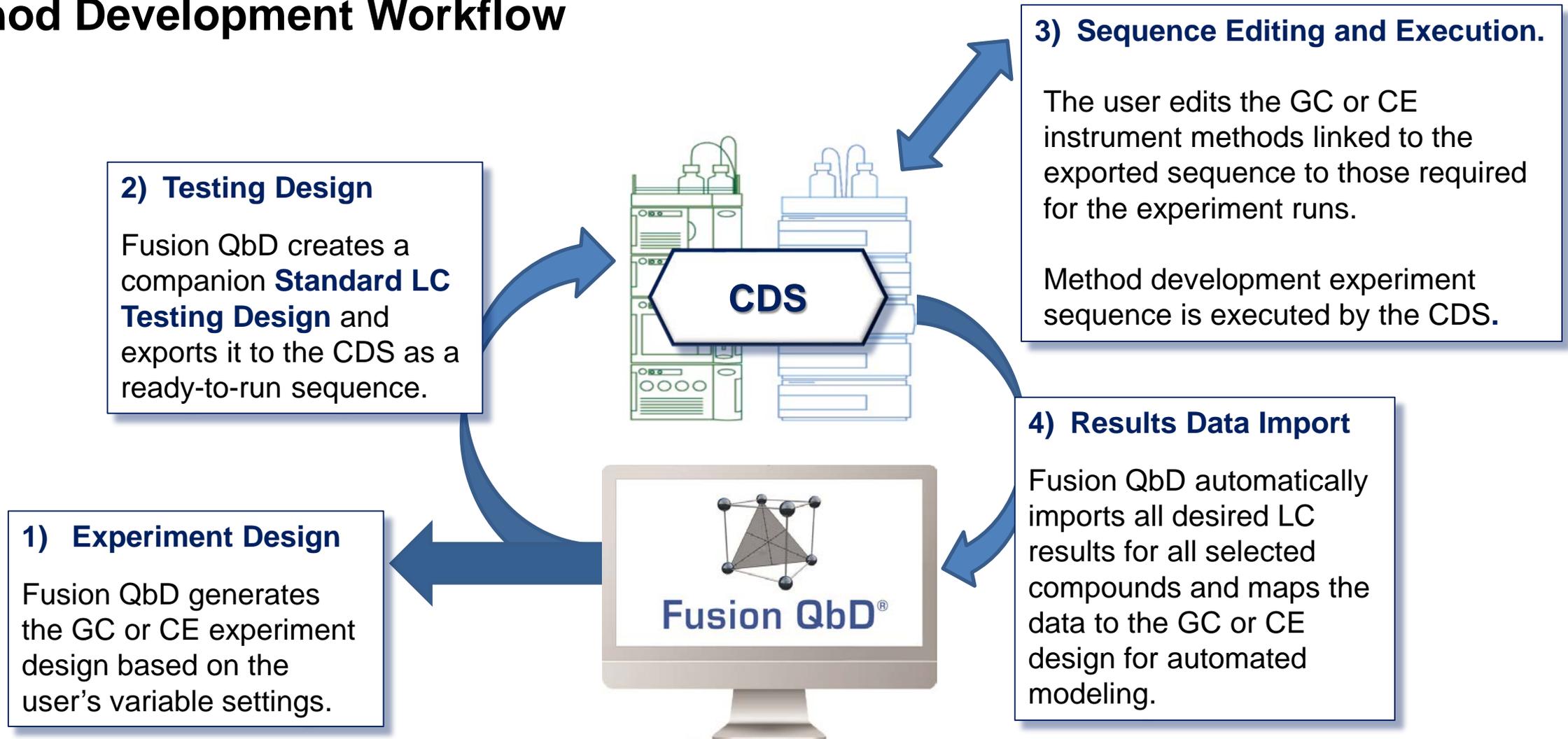
Experiment run samples are transferred to the LC for testing using the exported sequence.

### 4) Results Data Import

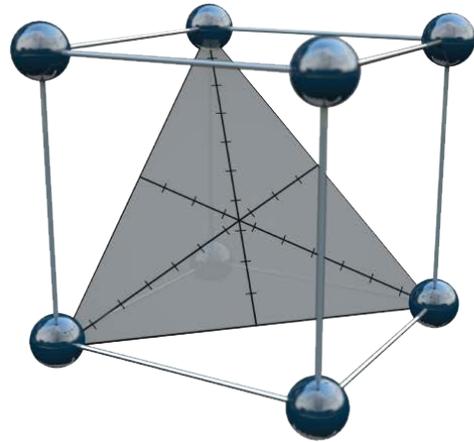
Fusion QbD automatically imports all desired LC results for all selected compounds – each result at each time point – from all runs and maps the data to the Dissolution design for automated modeling.



## Method Development Workflow



# *End of Presentation*



S-Matrix®

[www.smatrix.com](http://www.smatrix.com)