S-Matrix®

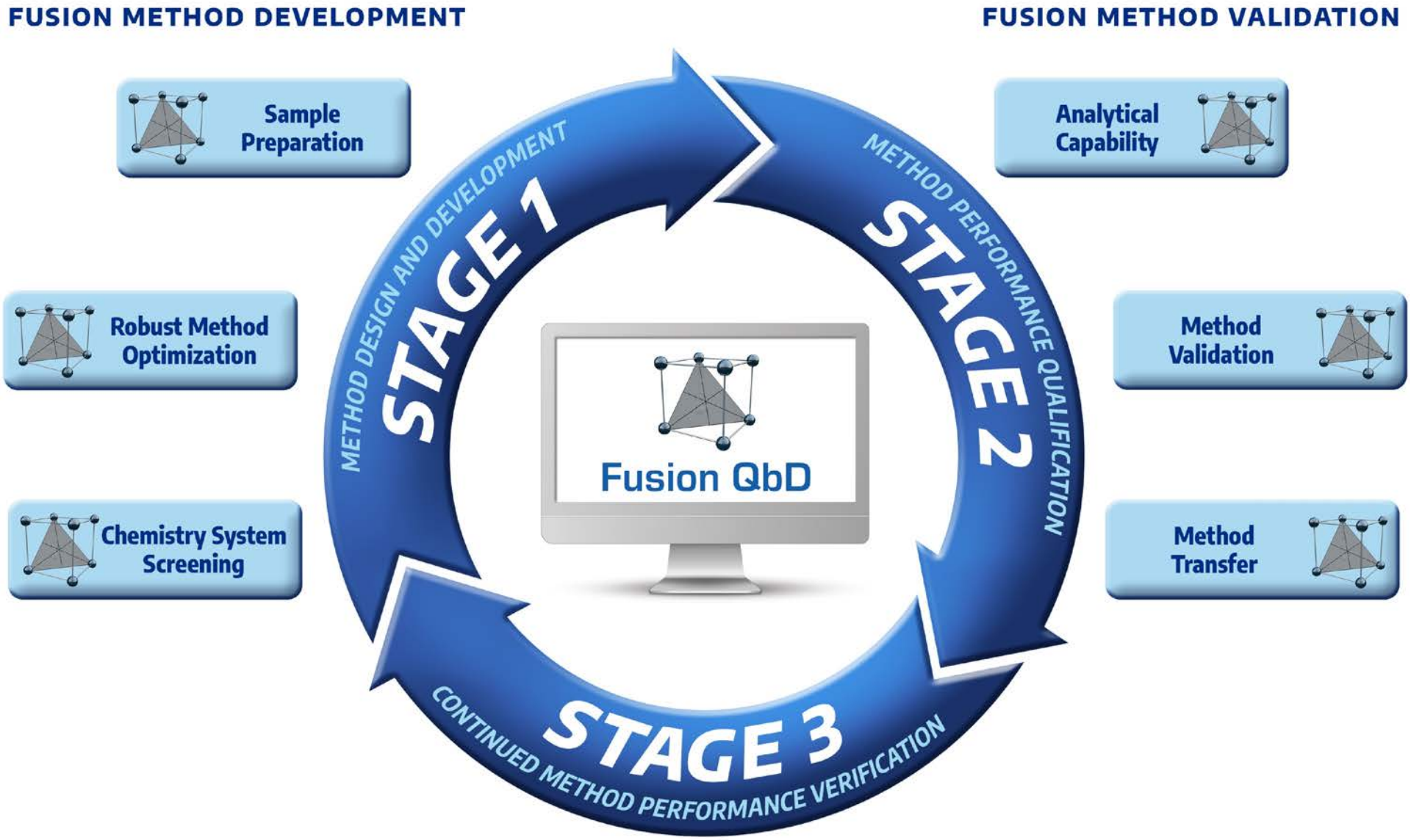
Fusion QbD

Case Study – Sample Preparation Method Development

S-Matrix Corporation

www.smatrix.com

A Complete Solution for APLM Stages 1 and 2



A Complete Solution for APLM Stage 1

Full Support for Part 11 Compliance

Citrix-Ready Certified

Fusion Process Development

- QbD Formulation and Process Development
- Non-LC Methods Development (e.g. GC, CE, Disso)
- Automated, Audited LC Testing and Data Acquisition
  Standard LC, Time Series, Respiratory

Full 21 CFR 11 Compliance Support

Why Compliance is Important!

FDA Statement* –

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

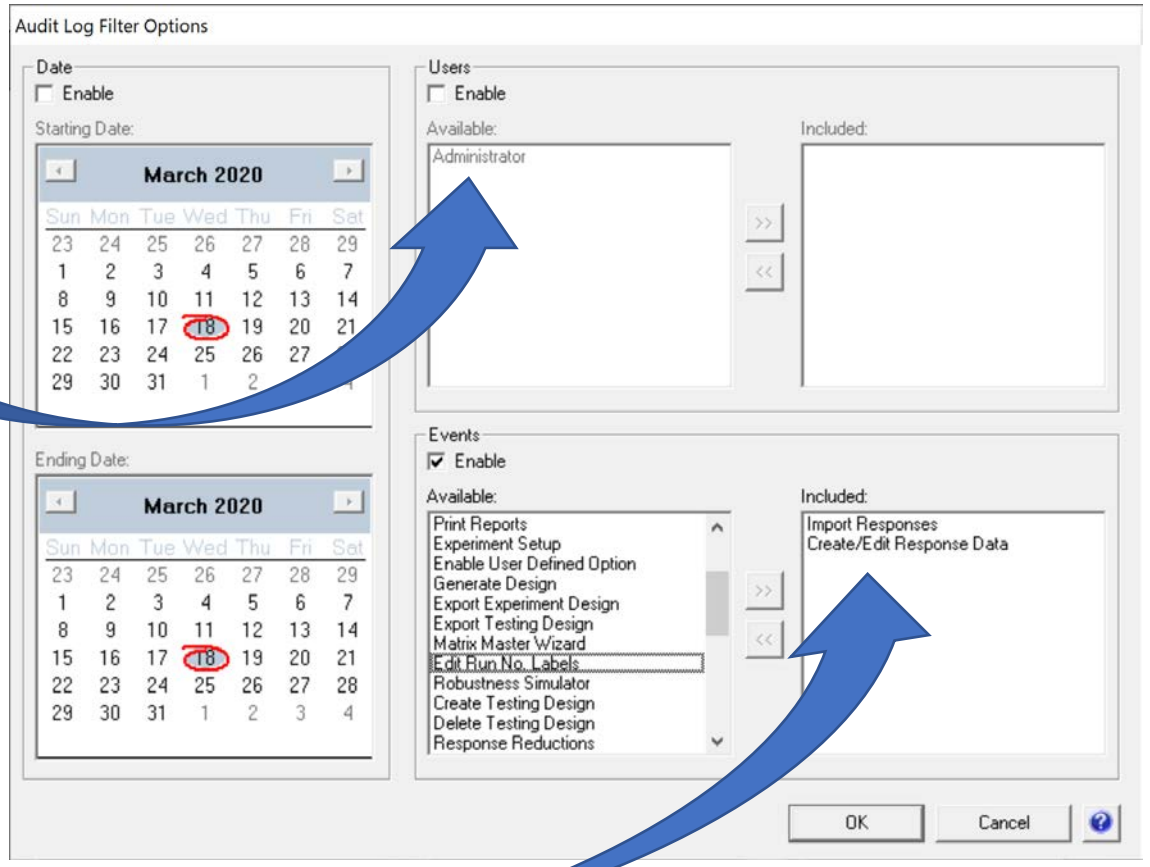
*** – USP Workshop – Enhanced Approaches for Analytical Procedure Lifecycle: An Alternative to Traditional Validation (Sept. 24-25, 2018)**

Full 21 CFR 11 Compliance Support

Why Audit Trail is Important!

Who entered this data – was the data modified?

What Empower Project did this data come from?



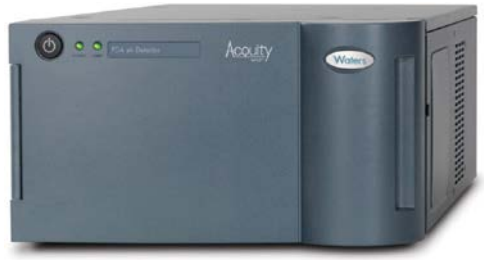
Project Software and Hardware Platform

Fusion QbD®

Empower™

H-Class UPLC

Acquity PDA



Acquity QDa

Sample Preparation Experiment Dataflow

1) Experiment Design

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

2) Testing Design

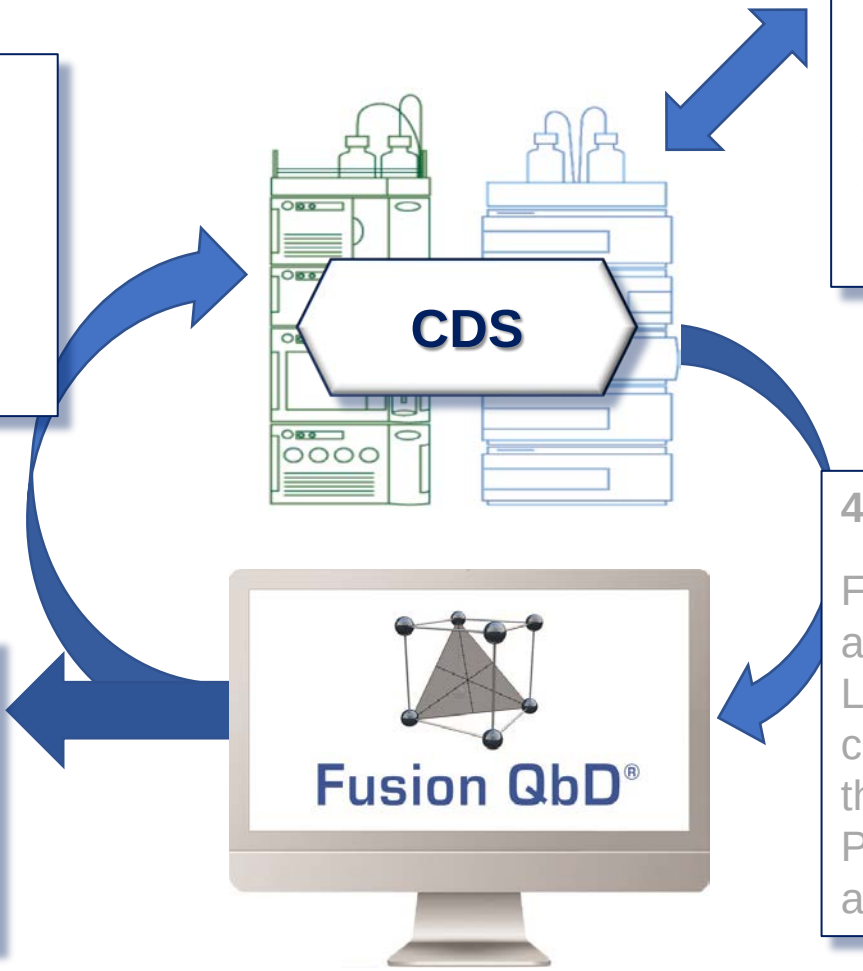
Fusion QbD creates a companion LC Testing Design and exports it to Empower as a ready-to-run Sample Set.

3) Sample Preparation Study Execution

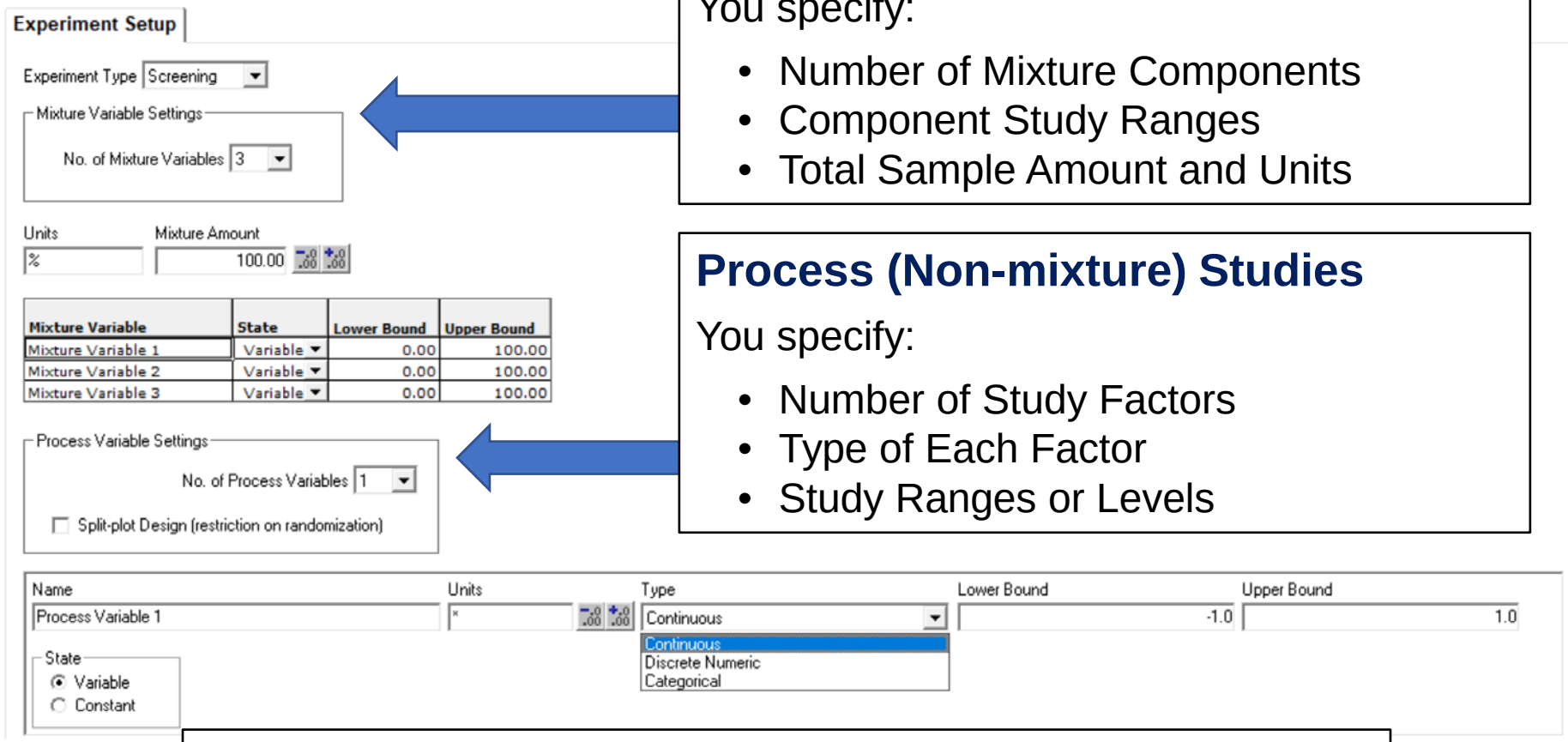
Experiment run samples transferred to LC for testing using the Fusion QbD Sample Set.

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.



Flexible Experiment Setup



Formulation (Mixture) Studies

You specify:

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

Process (Non-mixture) Studies

You specify:

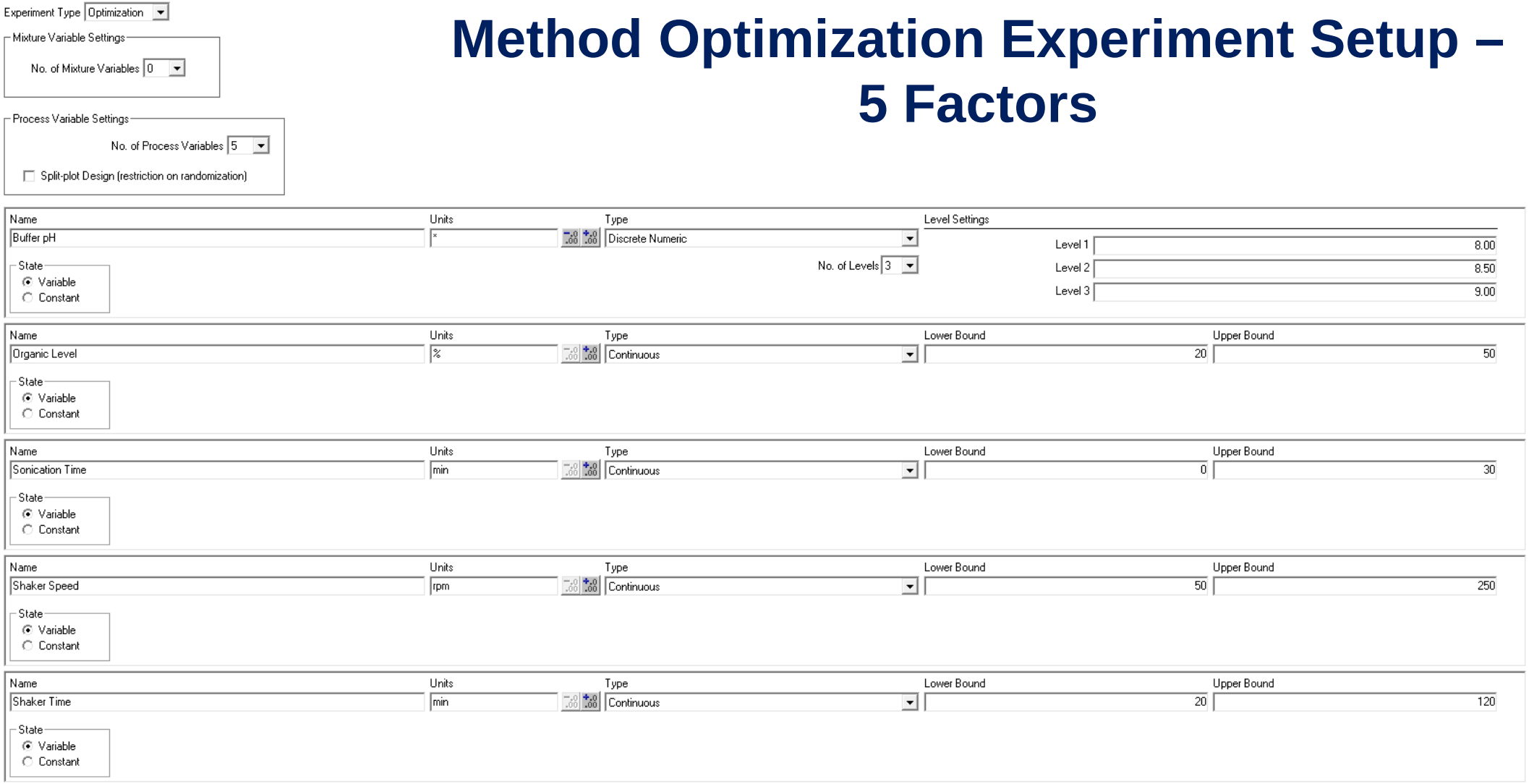
- Number of Study Factors
- Type of Each Factor
- Study Ranges or Levels

Combined Mixture-Process Studies

Enable you to characterize interactions between the two!

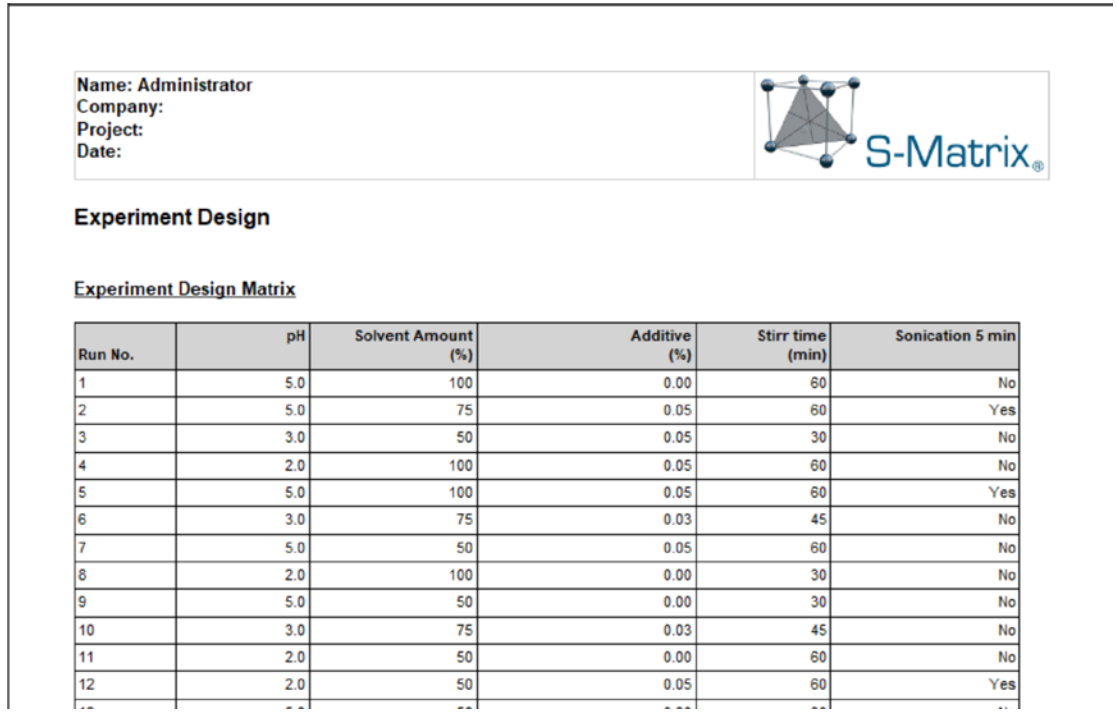
Complete Flexible Experiment Setup Template

Method Optimization Experiment Setup – 5 Factors



Automated Mode – 1-click Design Generation

Automatically Selects and Generates the Most Defensible and Efficient DOE Design



Name: Administrator
Company:
Project:
Date:

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Experiment Design

Experiment Design Matrix

Run No.	pH	Solvent Amount (%)	Additive (%)	Stirr time (min)	Sonication 5 min
1	5.0	100	0.00	60	No
2	5.0	75	0.05	60	Yes
3	3.0	50	0.05	30	No
4	2.0	100	0.05	60	No
5	5.0	100	0.05	60	Yes
6	3.0	75	0.03	45	No
7	5.0	50	0.05	60	No
8	2.0	100	0.00	30	No
9	5.0	50	0.00	30	No
10	3.0	75	0.03	45	No
11	2.0	50	0.00	60	No
12	2.0	50	0.05	60	Yes

Fusion QbD 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

Sample Preparation Experiment Dataflow

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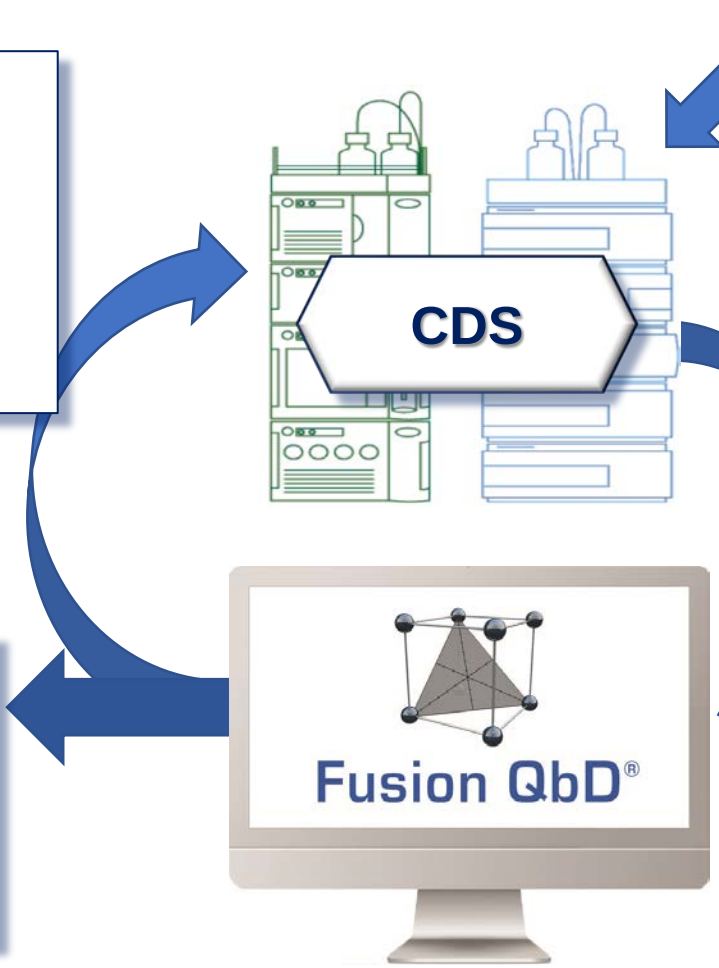


4) Results Data Import

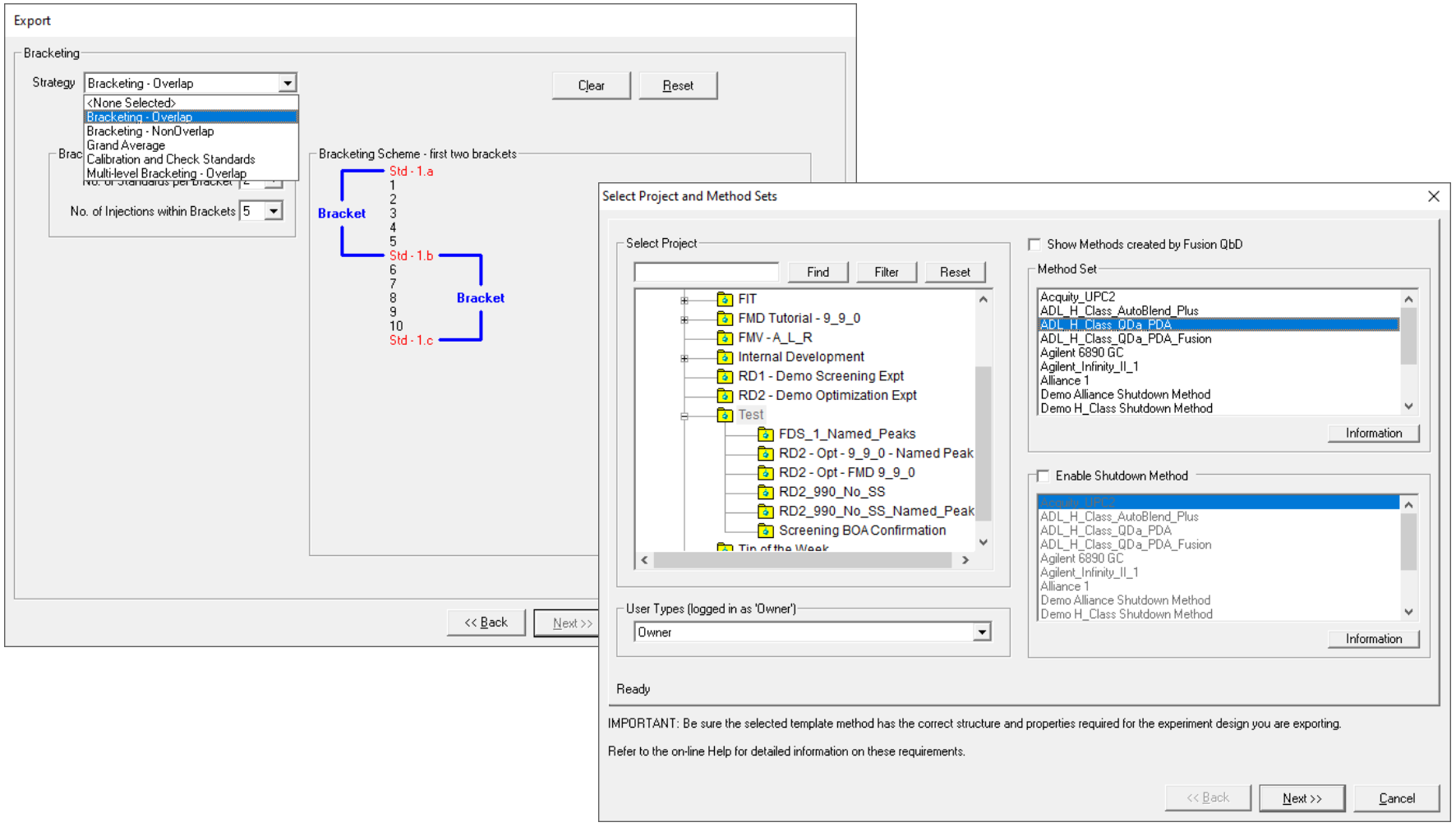
Fusion QbD automatically imports all LC results for all compounds and maps the data to the Sample Prep. Study design for automated modeling.

1) Experiment Design

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

Automated File-less Data Transfer

Automatically Export Ready-to-Run Testing Design to the CDS



Bi-directional

Auditing

Assures Data

Traceability

and Integrity!

Sample Preparation Experiment Dataflow

3) Sample Preparation Study Execution

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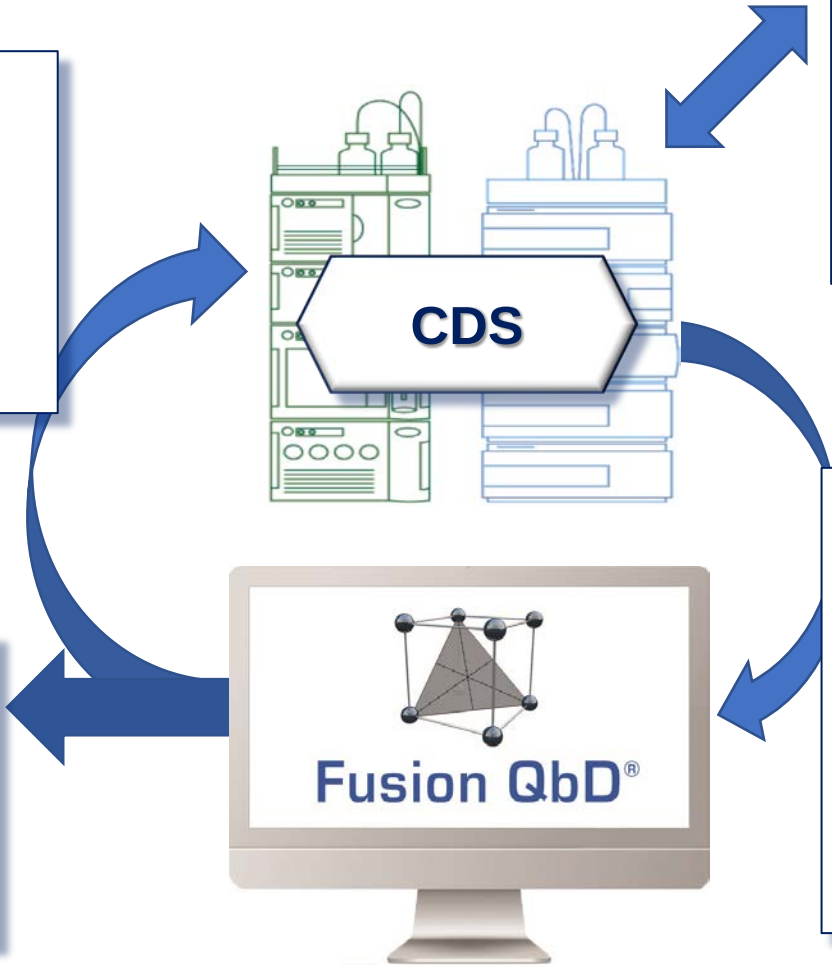

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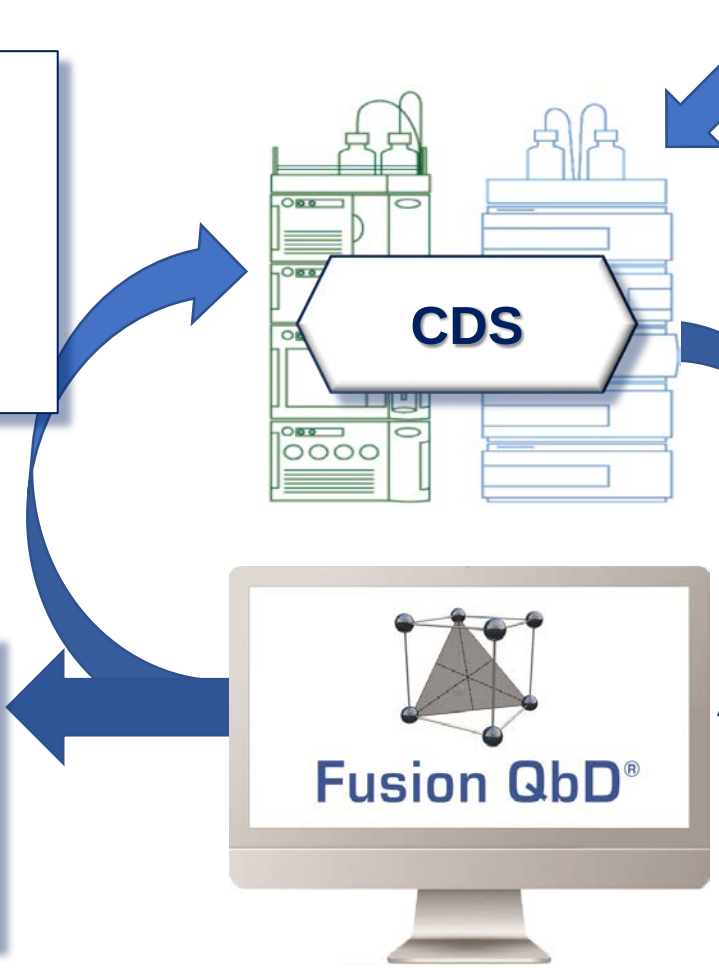

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4) Results Data Import

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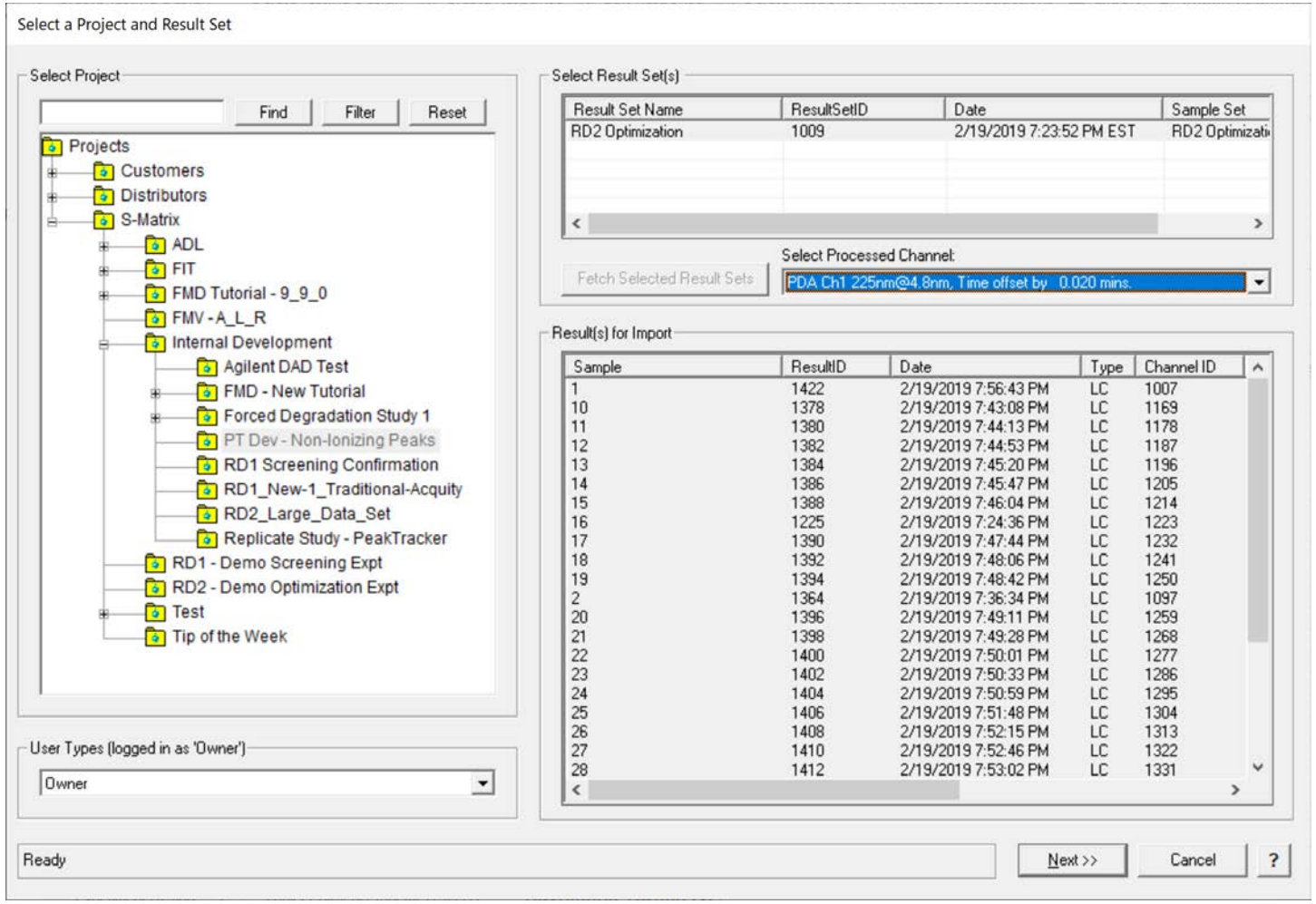
Automated File-less Data Transfer

Automatically Import All Required Results Data from CDS



Bi-directional

Auditing

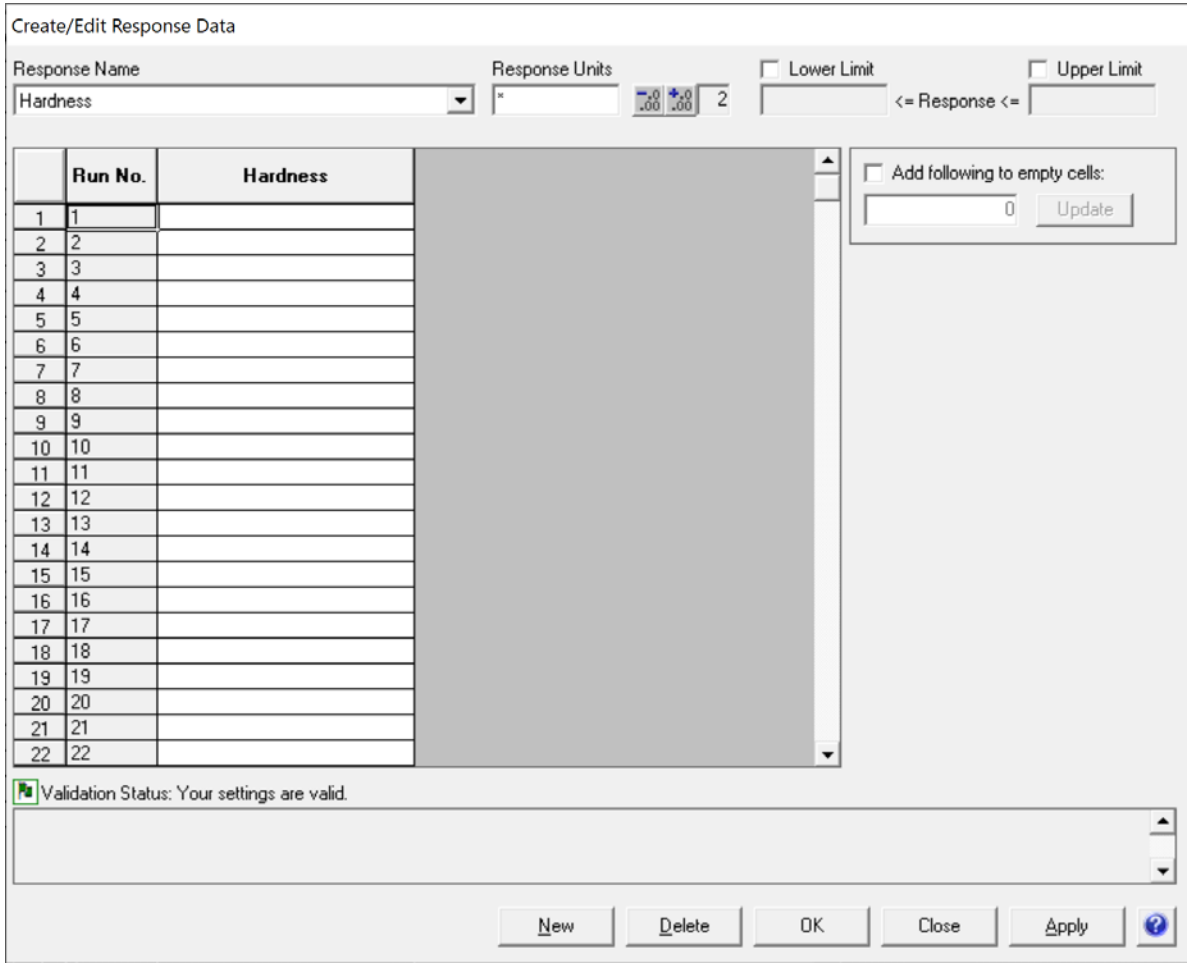
Assures Data

Traceability

and Integrity!

Directly Enter Collateral Data

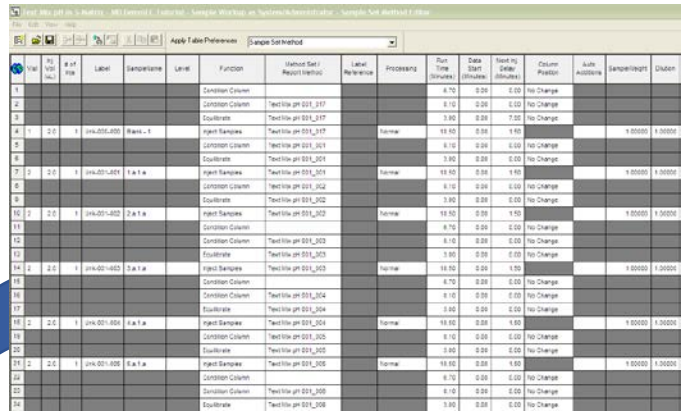
Directly Enter Non-CDS Generated Results Data

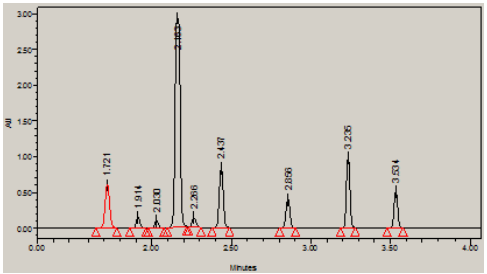


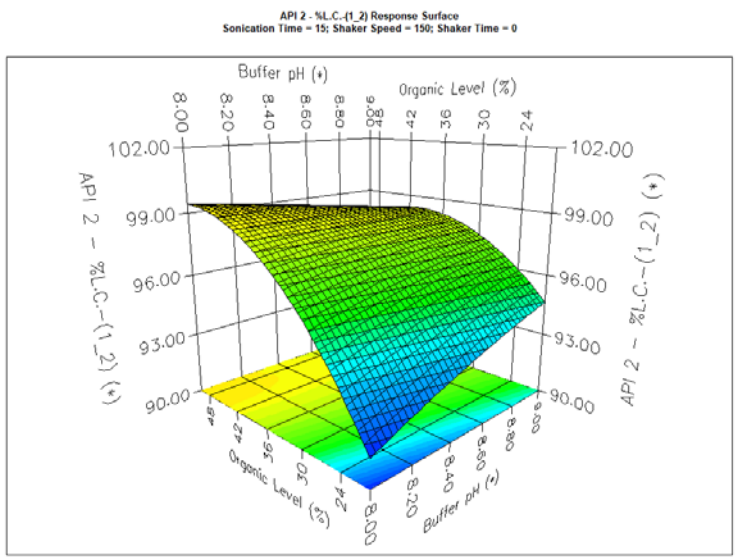
Full Auditing of Entered and Edited Data Assures Data Traceability and Integrity!

Automated Import and 1-Click Modeling

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







$$CQA = 9.3 + 4.2(pH) - 5.4(Add.)^2 + 12.7(Add*SolvAmt) + 1.3(SolvAmt*Sonic\Delta t) + 1.6[(\Delta pH)^2(Add.)] + \ldots$$

Linear Effect | Curvature Effect | Interaction Effects | Complex Effect

State-of-the-Art Modeling – Regulatory Accepted

U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

Example of a Resolution Model Eqn.

- Peak 3 resolution

$$R = 3.0607 + 0.4109(GT) - 0.3367(Temp) - 0.7772(pH) - 0.2013(pH)^2$$

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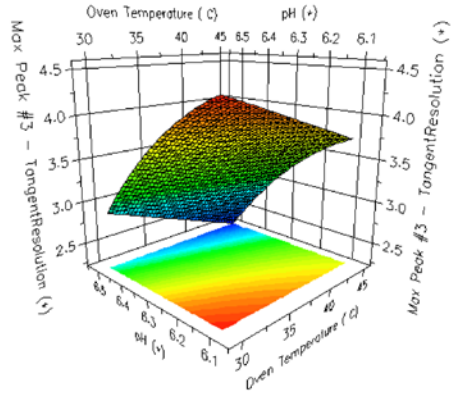
Example of a Resolution Model Eqn. Predicted Response



✓ Regulatory Acceptance of Fusion QbD

John F. Kauffman, Ph.D. and Daniel J. Mans, Ph.D., "*Experimental Design and Modeling to Improve HPLC Method Performance for Small Molecules*", FDA Division of Pharmaceutical Analysis, CASSS CMC Strategy Forum Europe 2015

Fusion QbD – Integrated Monte Carlo Robustness

Regulatory Acceptance of Monte Carlo Simulation Approach

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.

Fusion QbD – Integrated Monte Carlo Robustness

Regulatory Acceptance of Monte Carlo Simulation Approach

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.

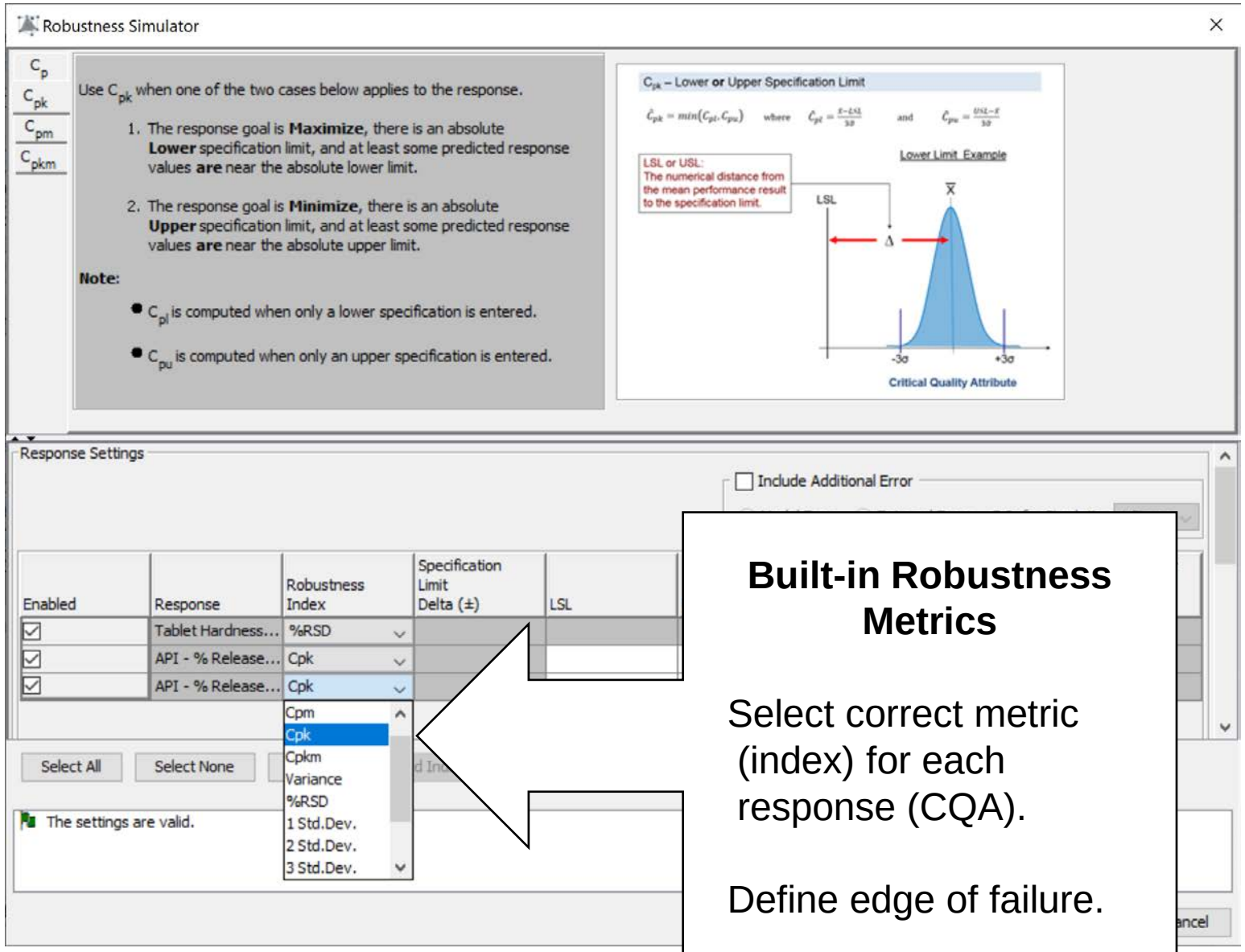
S_w is the within batch standard deviation (called the within sub group standard deviation in ISO) not the overall process standard deviation. It is usually estimated from a Shewhart mean and range control chart using the formula

ECA _AQCG_ SOP 03_APLM_v1.0_July 2018_Final_r1 Page 78 of 80

Analytical Procedure Lifecycle Management

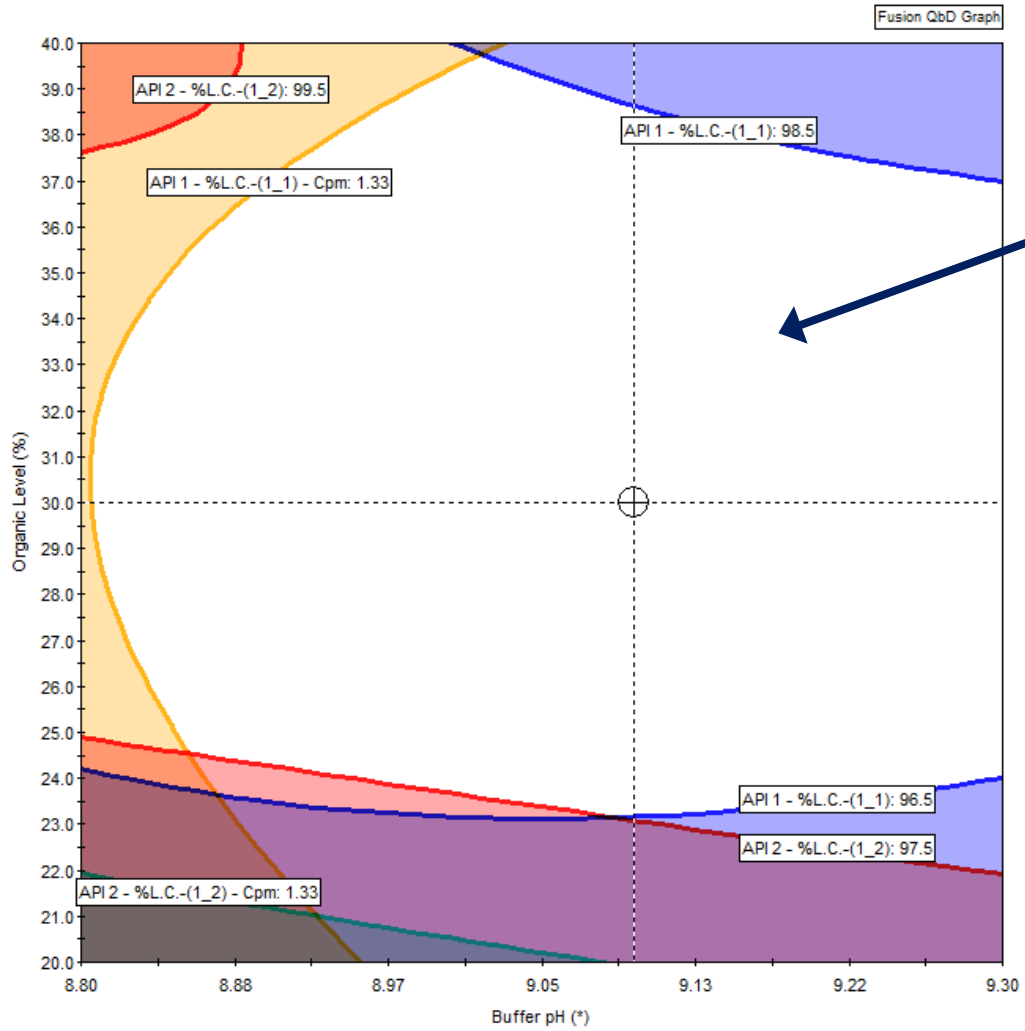
European Compliance Agency, Analytical Quality Control Group, July 2018, Final_r1

Fusion QbD – Integrated Monte Carlo Robustness



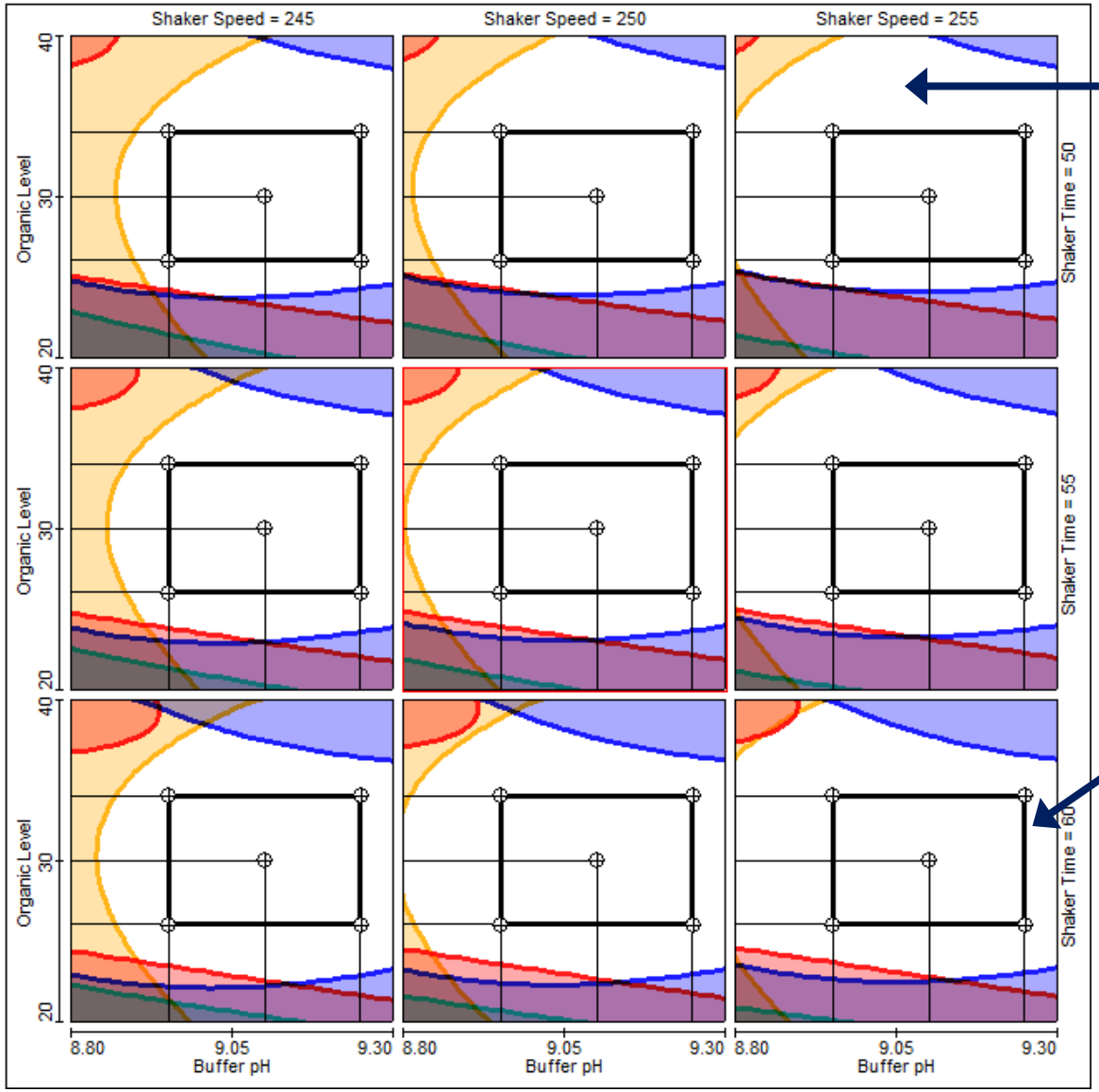
Multi-response Overlay Graph

Below is the ***Final Robust Method Operable Design Region (MODR)*** in which methods meet or exceed all critical **mean performance and robustness** goals simultaneously.



UNshaded Region in the graph is the Robust MODR

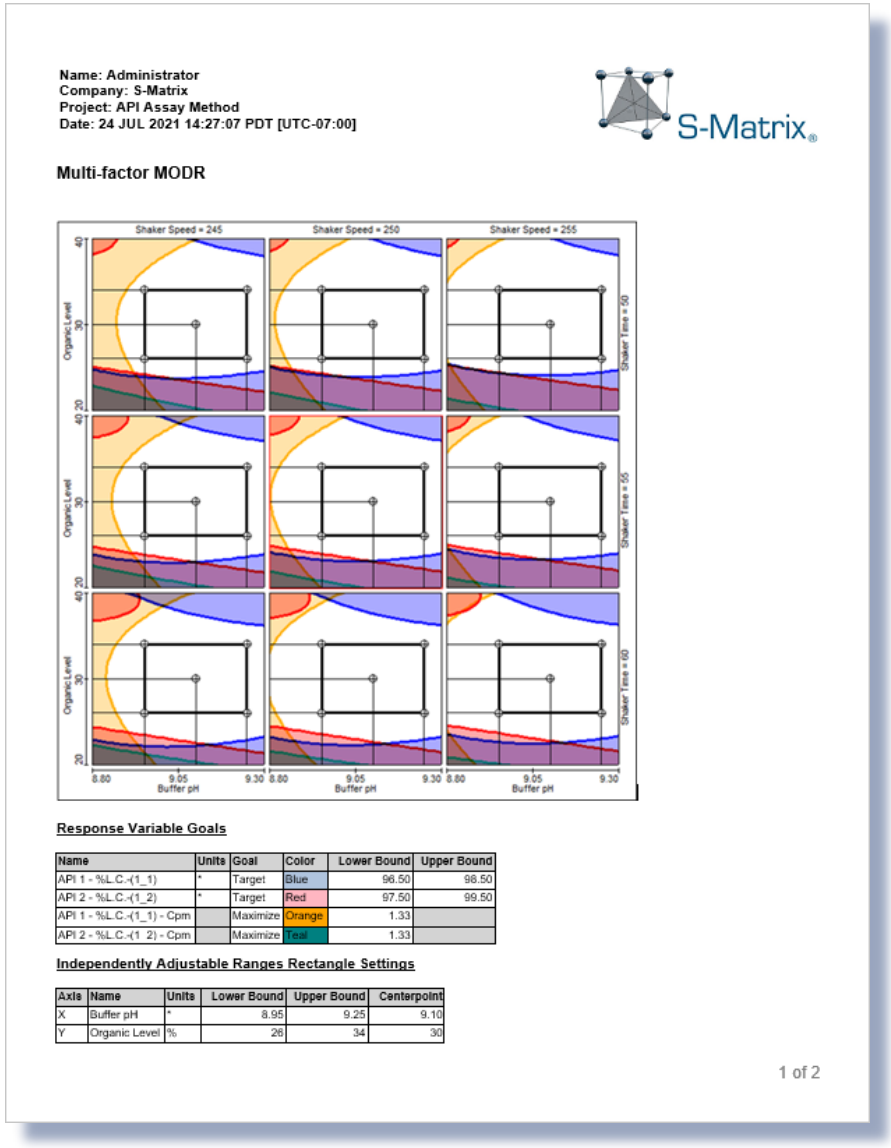
MODR Trellis Graph – 4 Study Factors



Unshaded Region in the graphs in combination with the Lower & Upper Bounds Of the Trellis Factors represent the 4-Factor Method Operable Design Region (MODR).

Rectangle represents the independently adjustable ranges of Buffer pH and Organic Level within the MODR.

Complete QbD Reporting



Name: Administrator
Company: S-Matrix
Project: API Assay Method
Date: 24 JUL 2021 14:27:07 PDT [UTC-07:00]

S-Matrix®

Multi-factor MODR

Response Variable Goals

Name	Units	Goal	Color	Lower Bound	Upper Bound
API 1 - %L.C.-(1_1)	%	Target	Blue	96.50	98.50
API 2 - %L.C.-(1_2)	%	Target	Red	97.50	99.50
API 1 - %L.C.-(1_1) - Cpm		Maximize	Orange	1.33	
API 2 - %L.C.-(1_2) - Cpm		Maximize	Teal	1.33	

Independently Adjustable Ranges Rectangle Settings

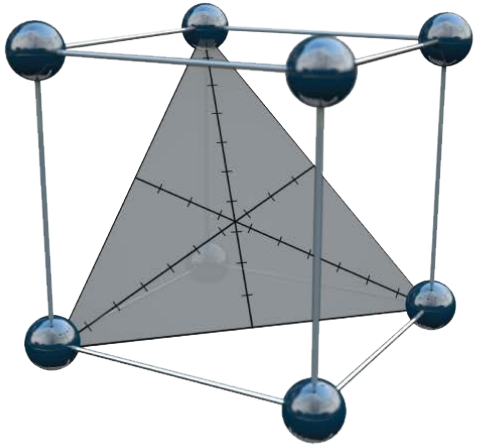
Axis	Name	Units	Lower Bound	Upper Bound	Centerpoint
X	Buffer pH		8.95	9.25	9.10
Y	Organic Level	%	26	34	30

1 of 2

Report Output in Multiple Formats

- MS Excel
- MS Word
- PDF
- …

End of Presentation



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